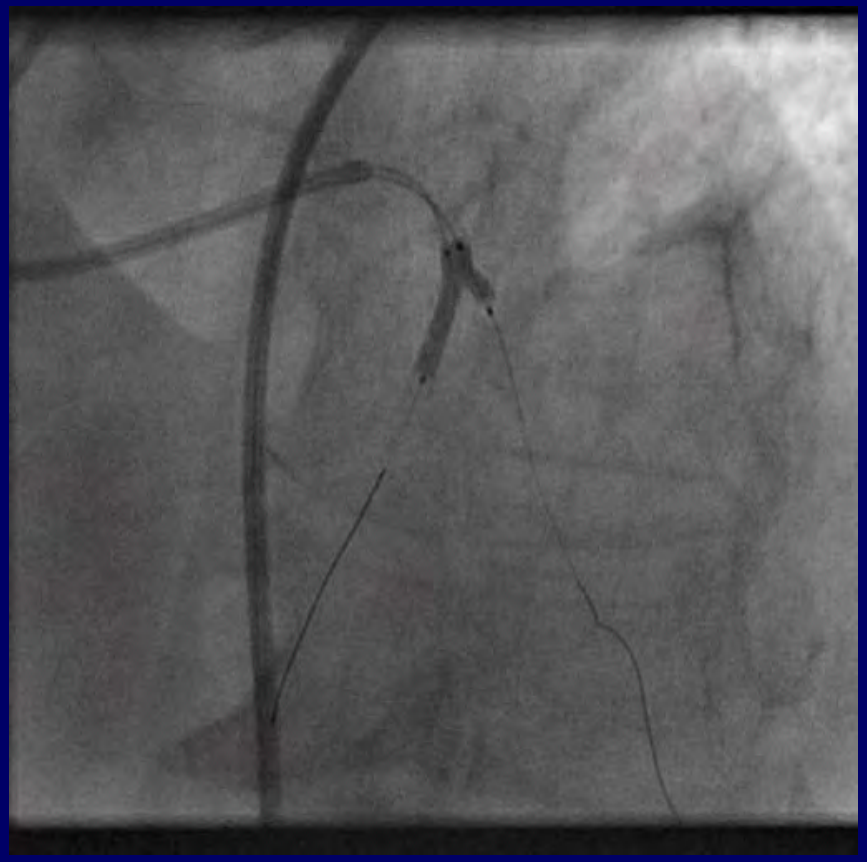
Interventional Cardiology



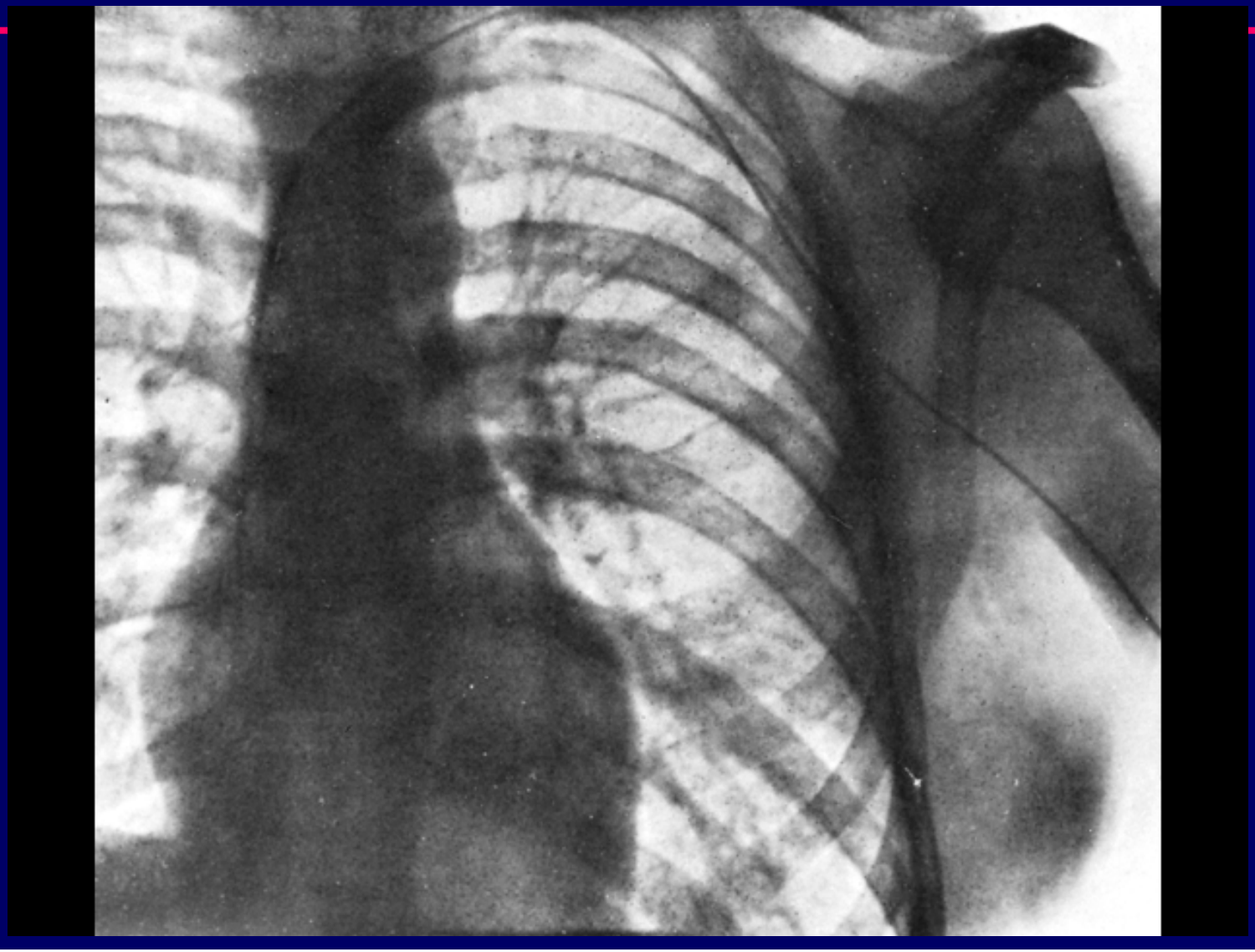
חיים דננברג
מערך הלב
הדסה עין-כרם

History

- 1844- Claude Bernard. Introduced catheter through carotid artery of a horse into left ventricle to measure temperature.
- 1929- Werner Forsmann. Introduced urologic catheter from brachial vein into right atrium.

WERNER FORSSMANN, M.D.

History



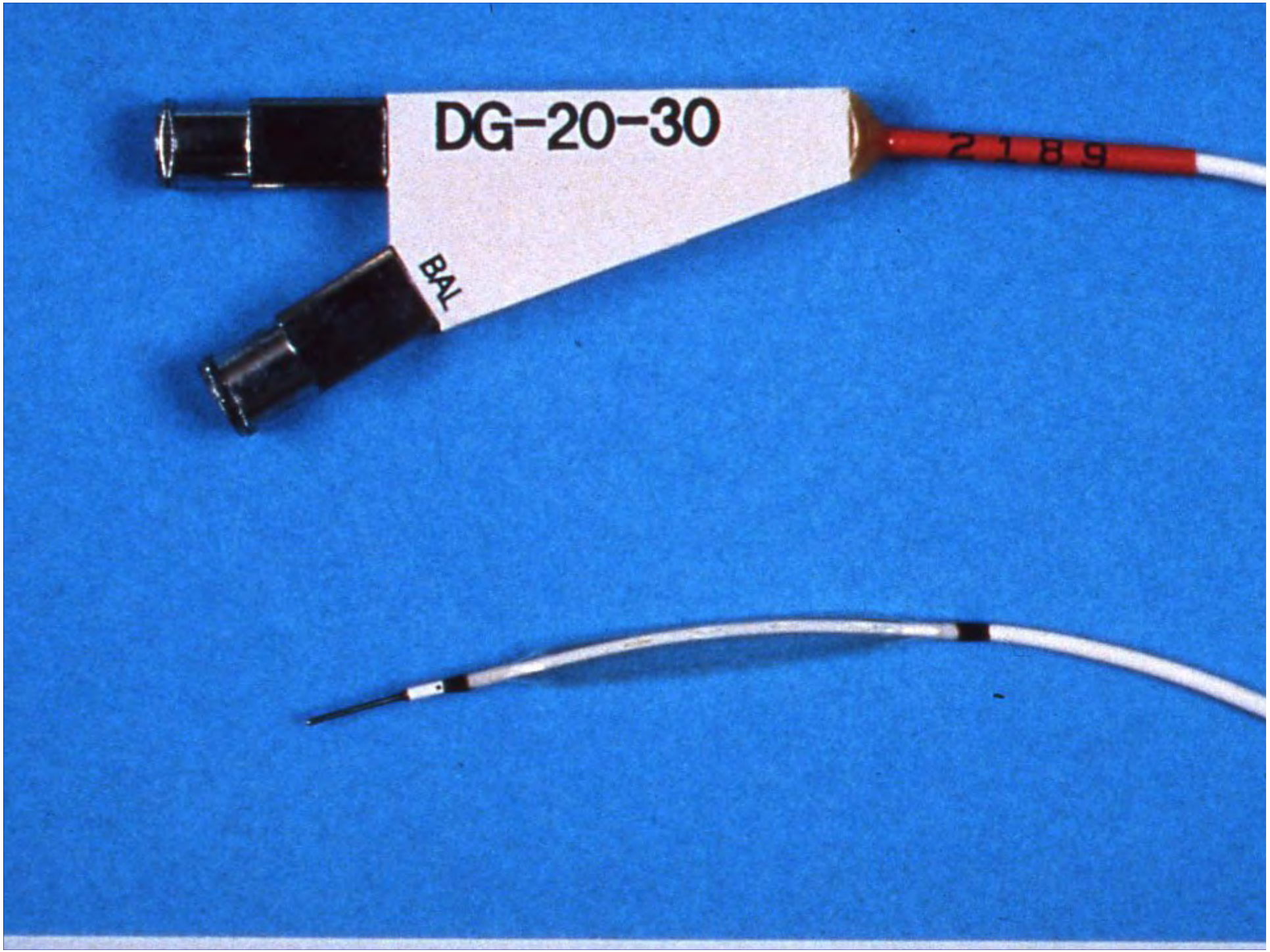
History

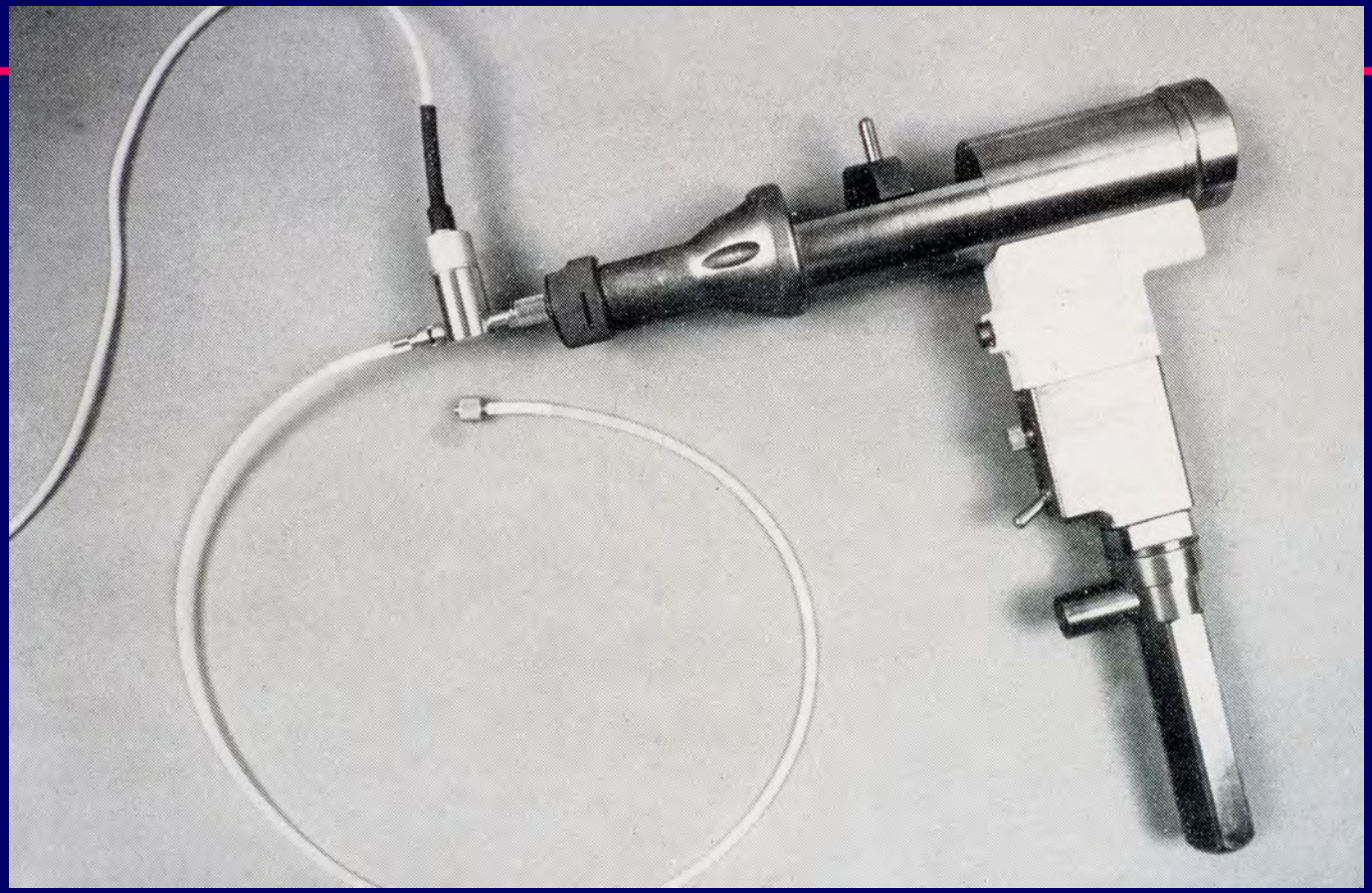
- 1940s- Cournand. Systematic investigation of right heart pressures in normal and diseased hearts.
- 1958- Sones. Established technique for selective angiography of the coronary arteries.
- 1964 - Dotter. First balloon angioplasty for peripheral artery stenosis.
- 1967 – Judkins. Femoral approach coronary angiography.
- 1977- Greuntzig. First human angioplasty for coronary artery stenosis.

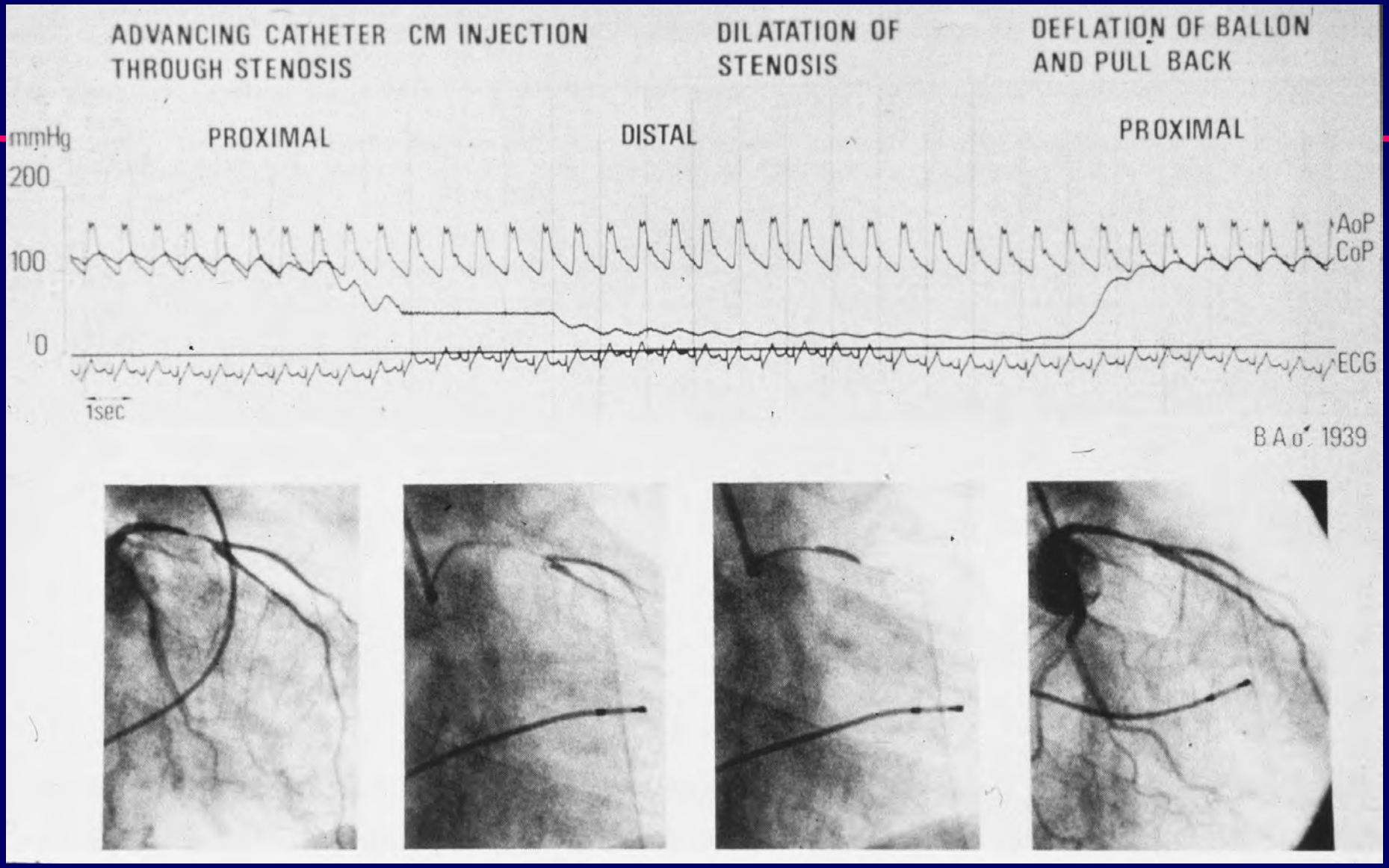
The age of Intervention

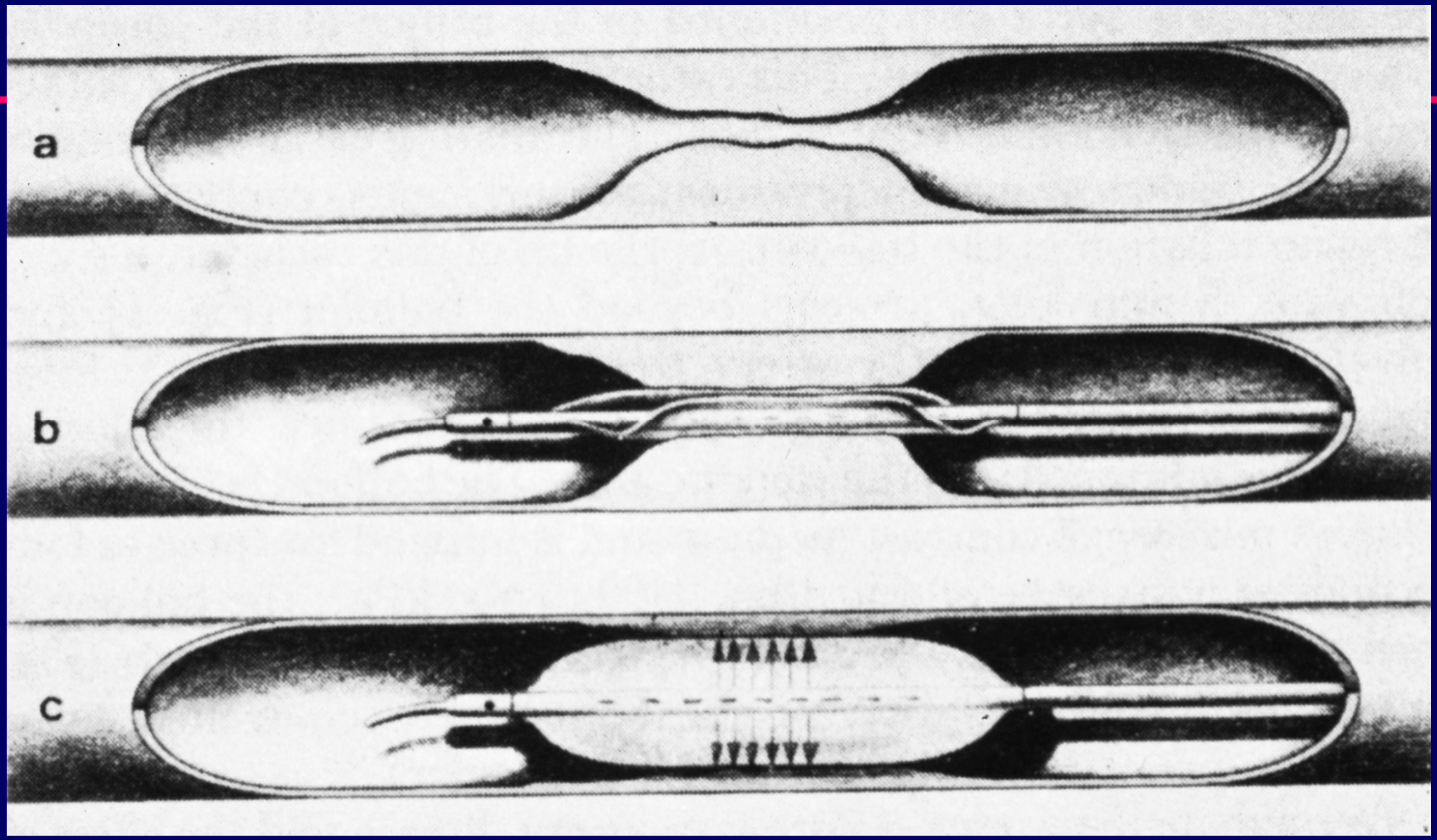
PTCA - 1977

Percutaneous Transluminal Coronary Angioplasty


DG-20-30
BAL
2189




ADVANCING CATHETER THROUGH STENOSIS
CM INJECTION
DILATATION OF STENOSIS
DEFLATION OF BALLON AND PULL BACK
mmHg
PROXIMAL
DISTAL
PROXIMAL
200
100
0
AoP
CoP
ECG
1sec
B A o. 1939


a
b
c

Mechanism of angioplasty

i. Compression and redistribution of plaque
ii. Embolization of plaque components
iii. Arterial enlargement (aneurysm formation)
iv. Disruption of plaque and arterial wall
v. Intimal tears and dissections

Indication for PTCA according Andreas Gruntzig View

Proximal stenosis

Good left ventricular function

No left main

No calcified lesion

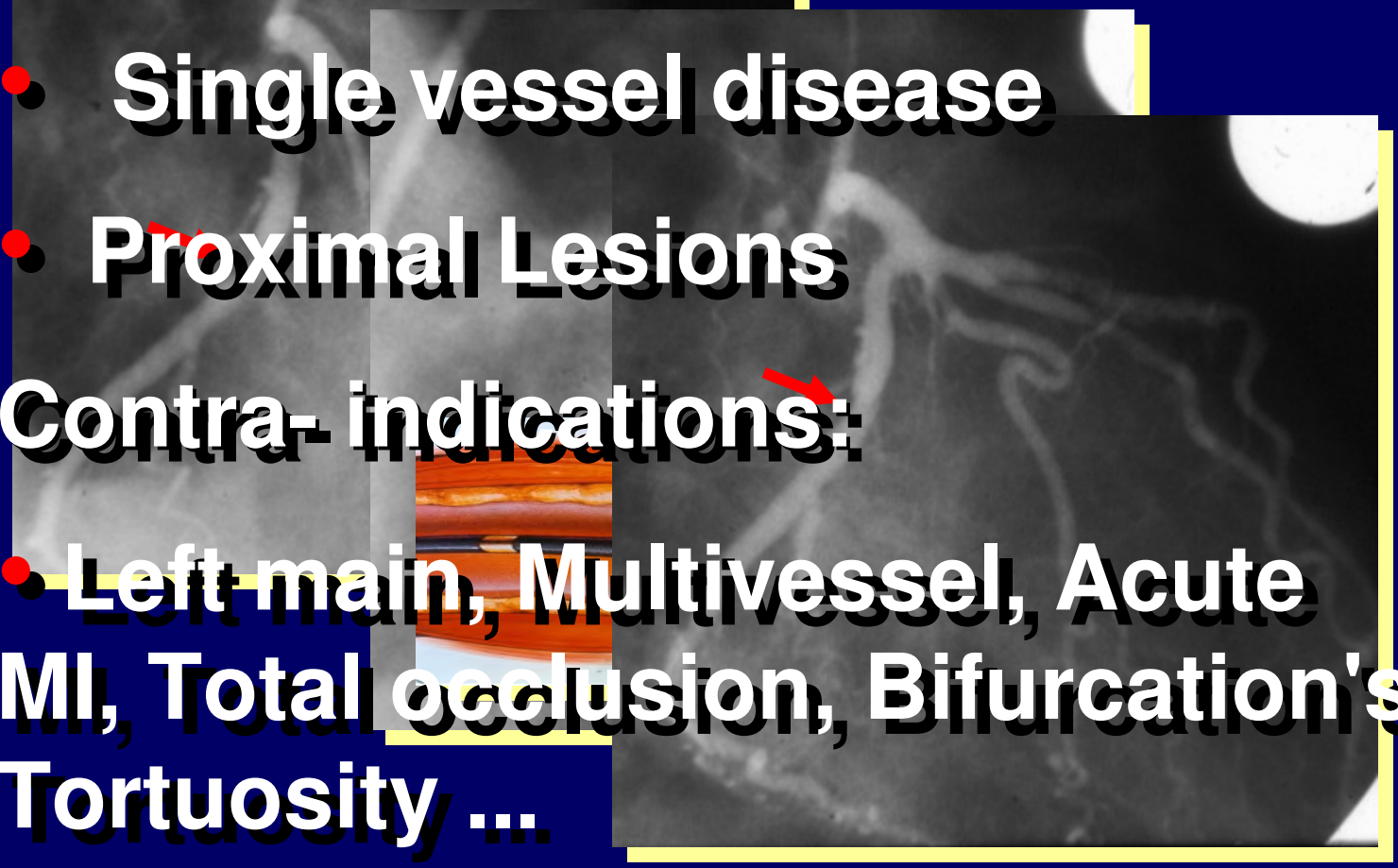
PTCA

Indications for PTCA:

- Single vessel disease
- Proximal Lesions

Contra- indications:

- Left main, Multivessel, Acute MI, Total occlusion, Bifurcation's, Tortuosity ...



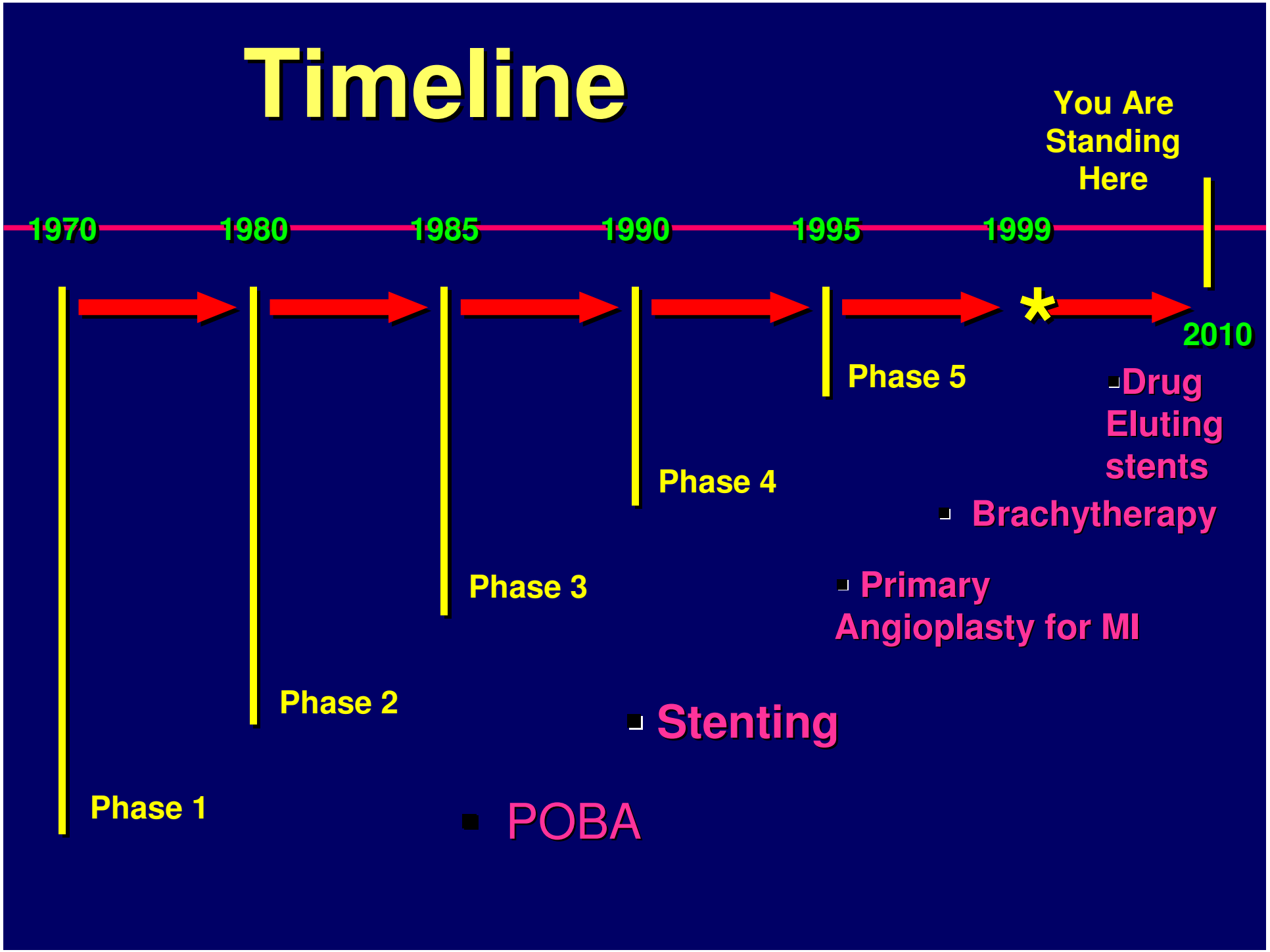
Indication 2010 for PCI

There are in general no contraindications

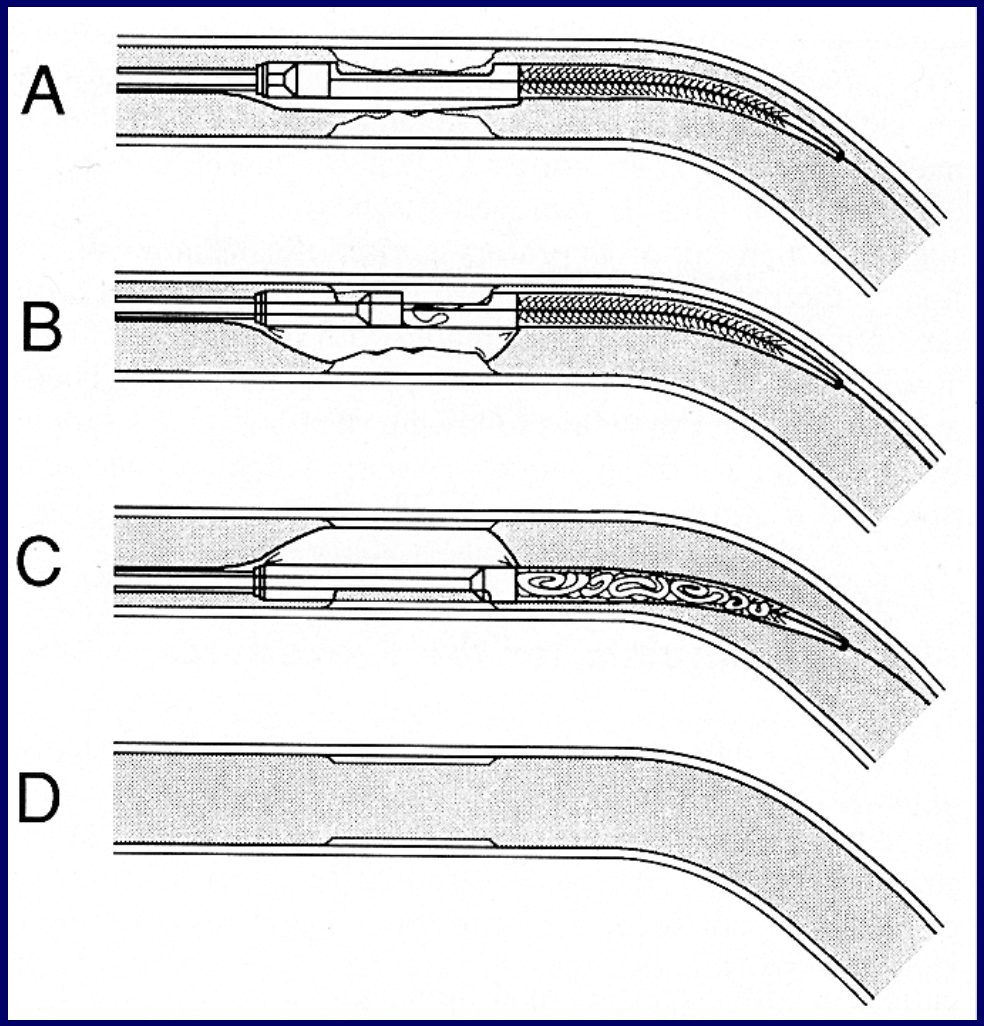
"…The only indication for CABG is a failed PTCA…"
G.Hartzler

A wide variety of balloons

Timeline


You Are Standing Here
1970
1980
1985
1990
1995
1999
2010
*
Phase 1
Phase 2
Phase 3
Phase 4
Phase 5
POBA
Stenting
Primary Angioplasty for MI
Brachytherapy
Drug Eluting stents

Simpson 1986: Coronary directional atherectomy in humans



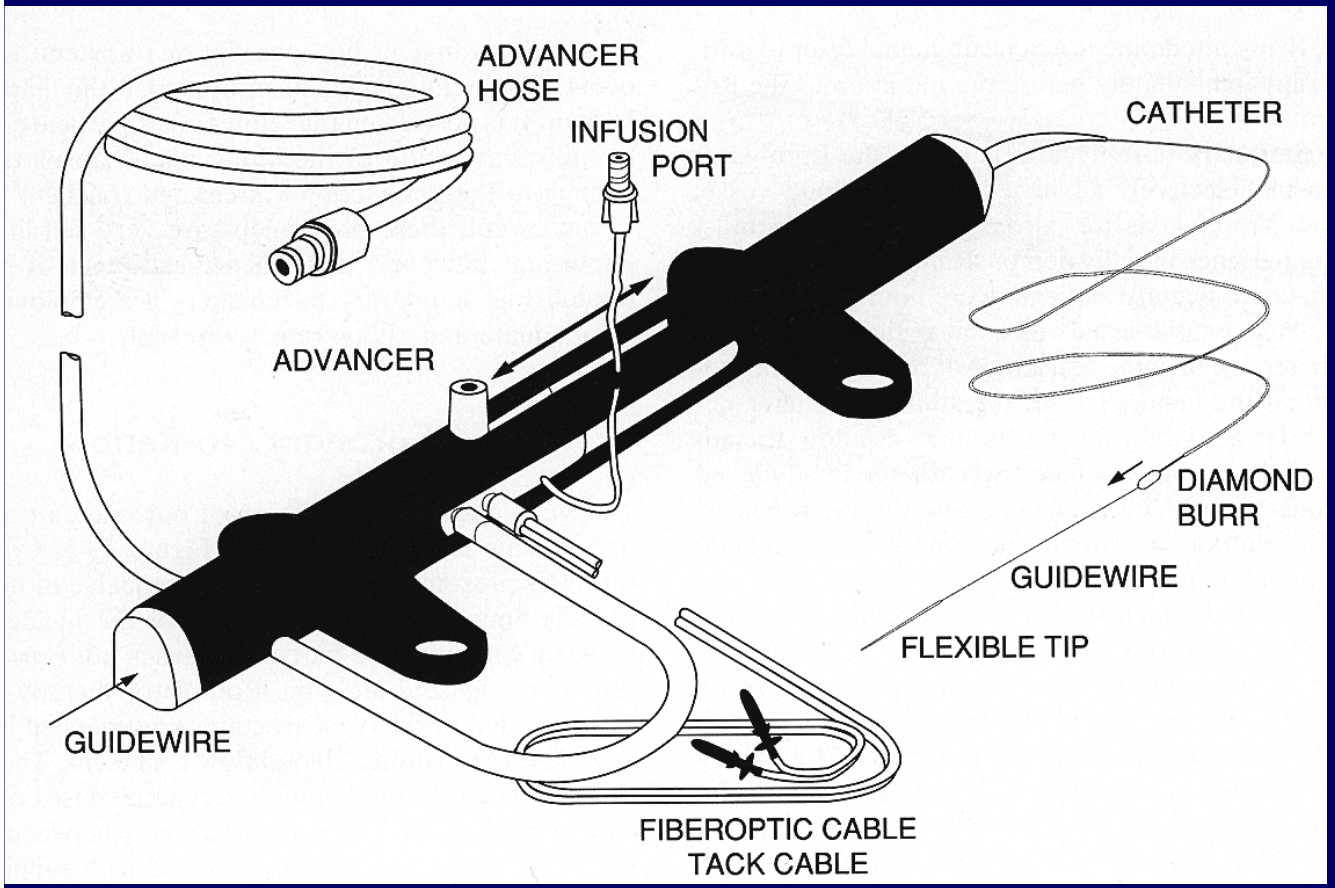
Directional Coronary Atherectomy

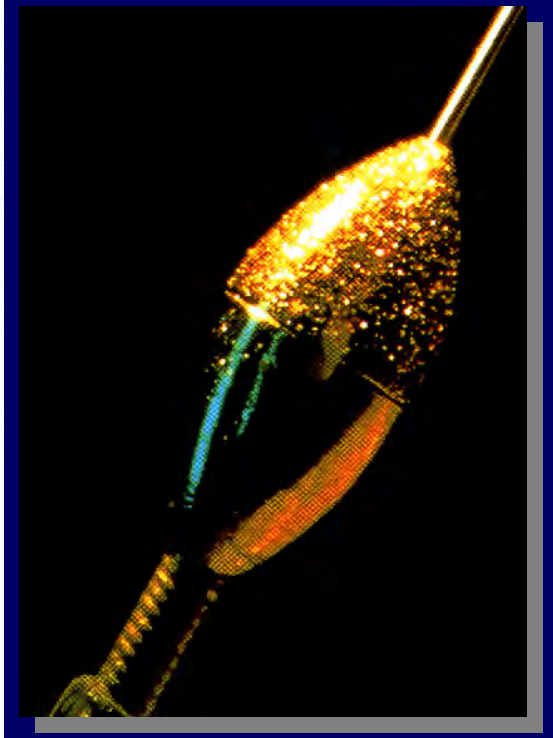
→ Debulking gives Less elastic recoil
→ Less dissection
→ Wider lumen
→ Smoother lumen

Applications of DCA

- Type A lesion in large vessel (> 3mm)
- Severely eccentric lesion
- Abnormal contour (ulceration, flap, limited dissection)
- Ostial lesion
- Large bifurcation lesion
- Moderately lenghthy lesion in large vessel
- Salvage for failed PTCA

Auth 1988: rotablator

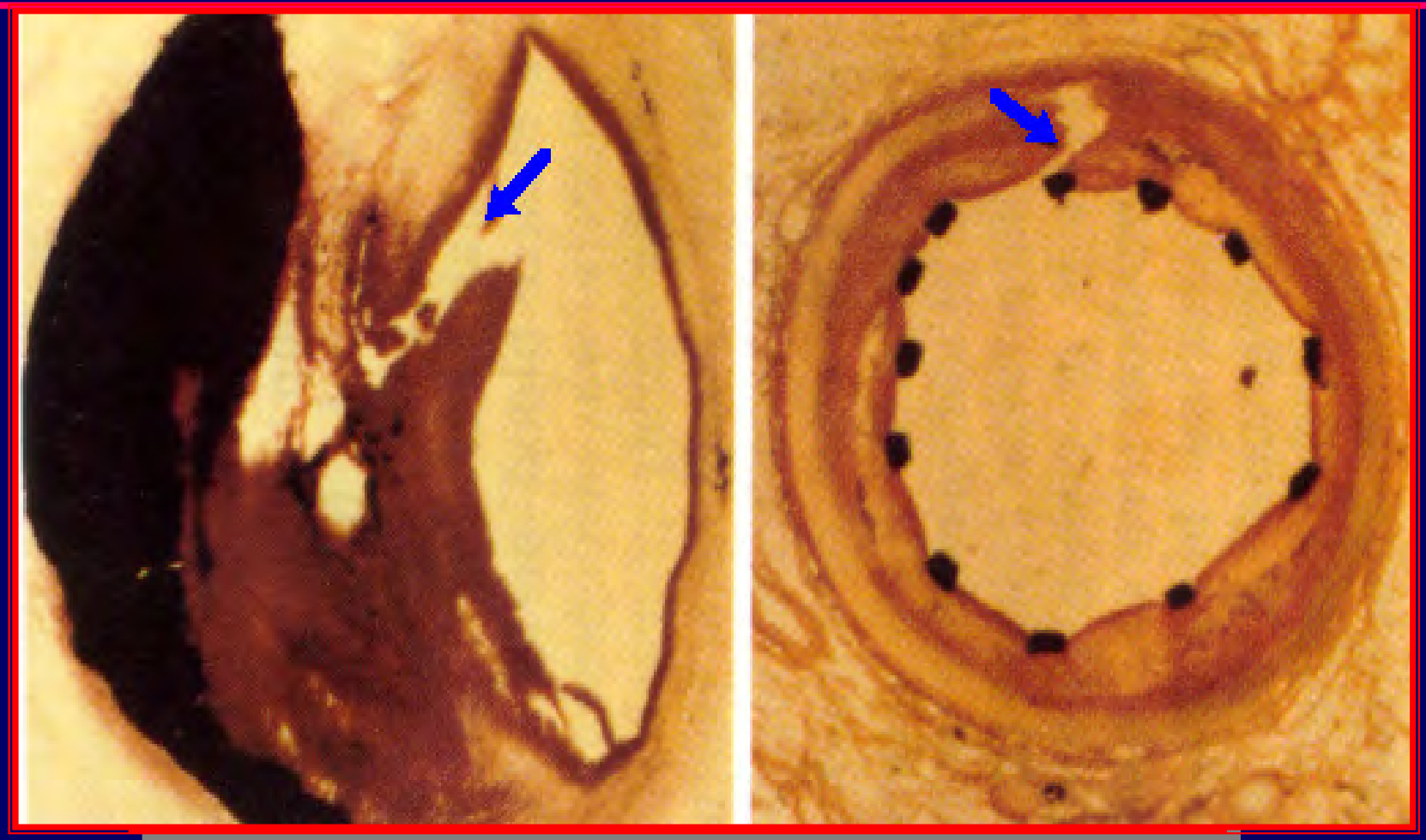




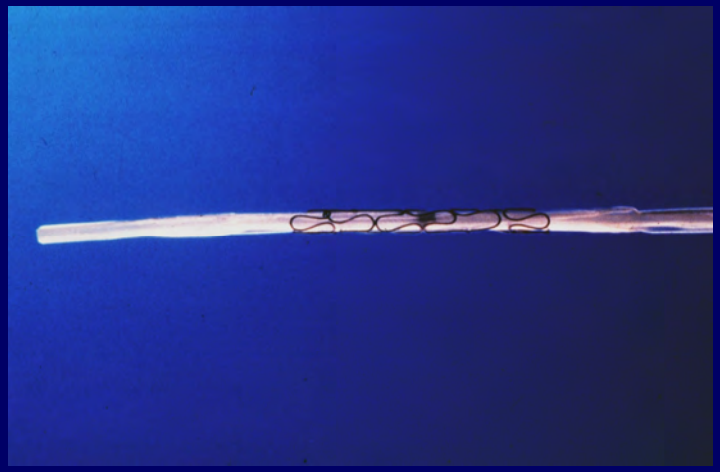
Applications for Rotablator

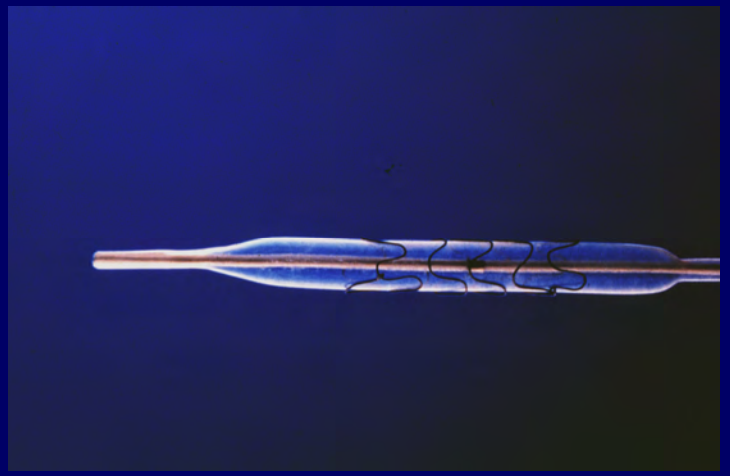
- Calcified lesions
- Tortuous lesions
- Ostial lesions
- Undilatable lesions
- Debulking in Instent restenosis

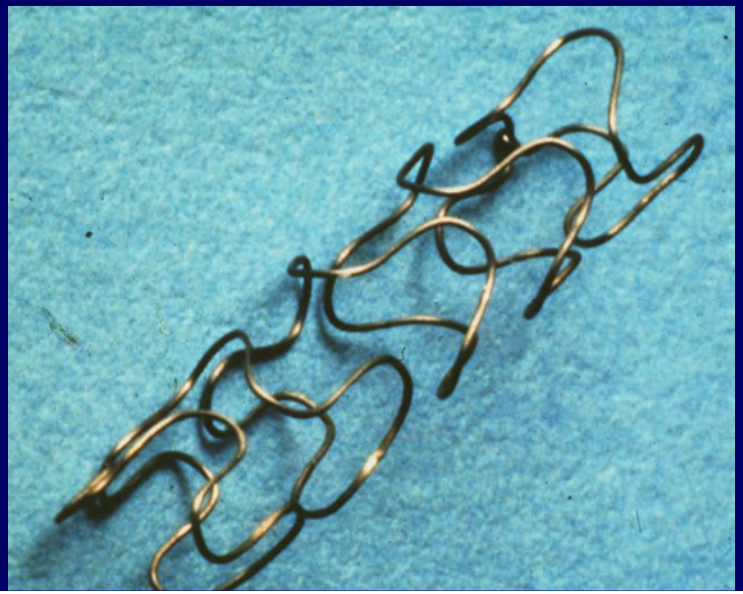
Coronary Dissections

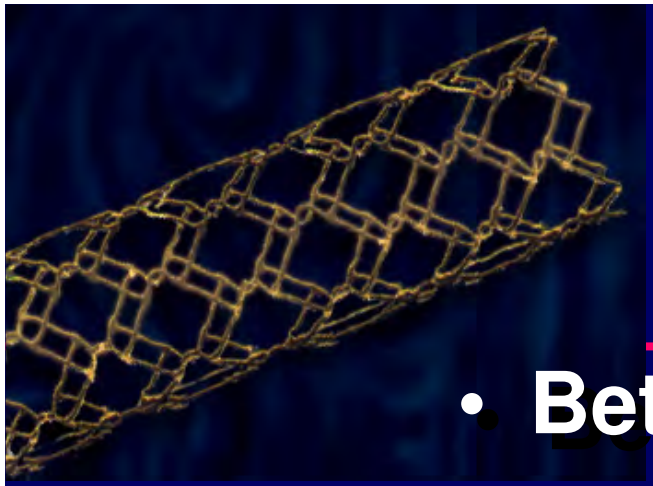


Sigwart 1986: coronary stenting

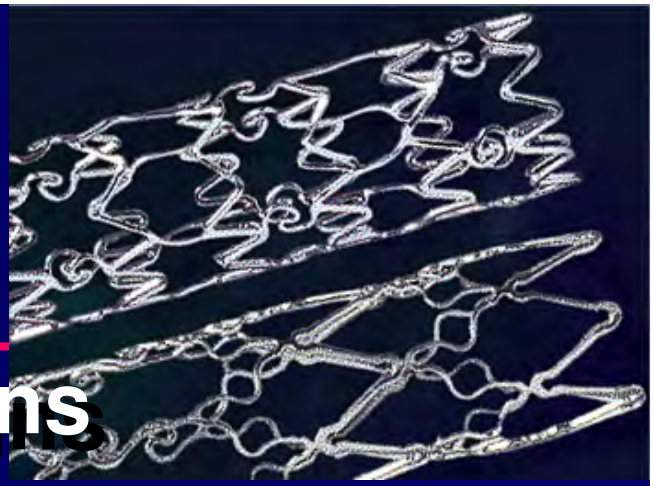




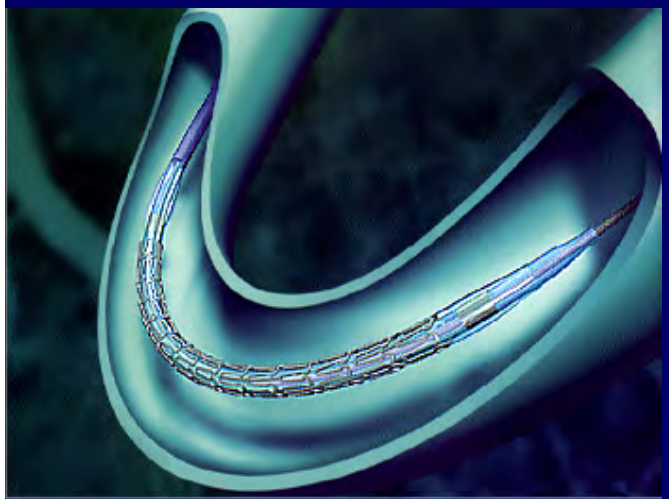


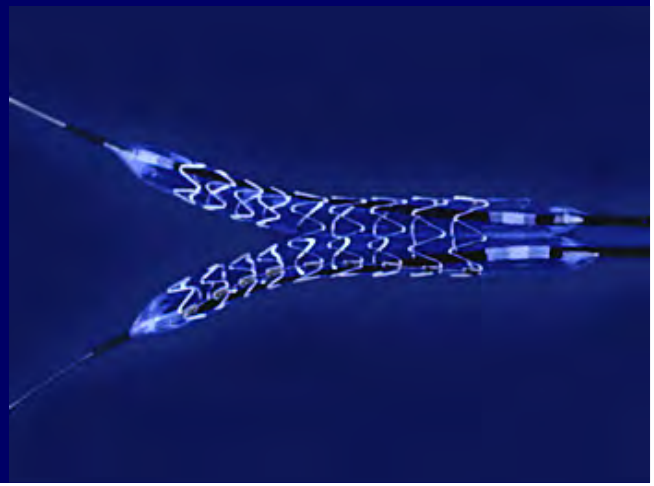


Stents



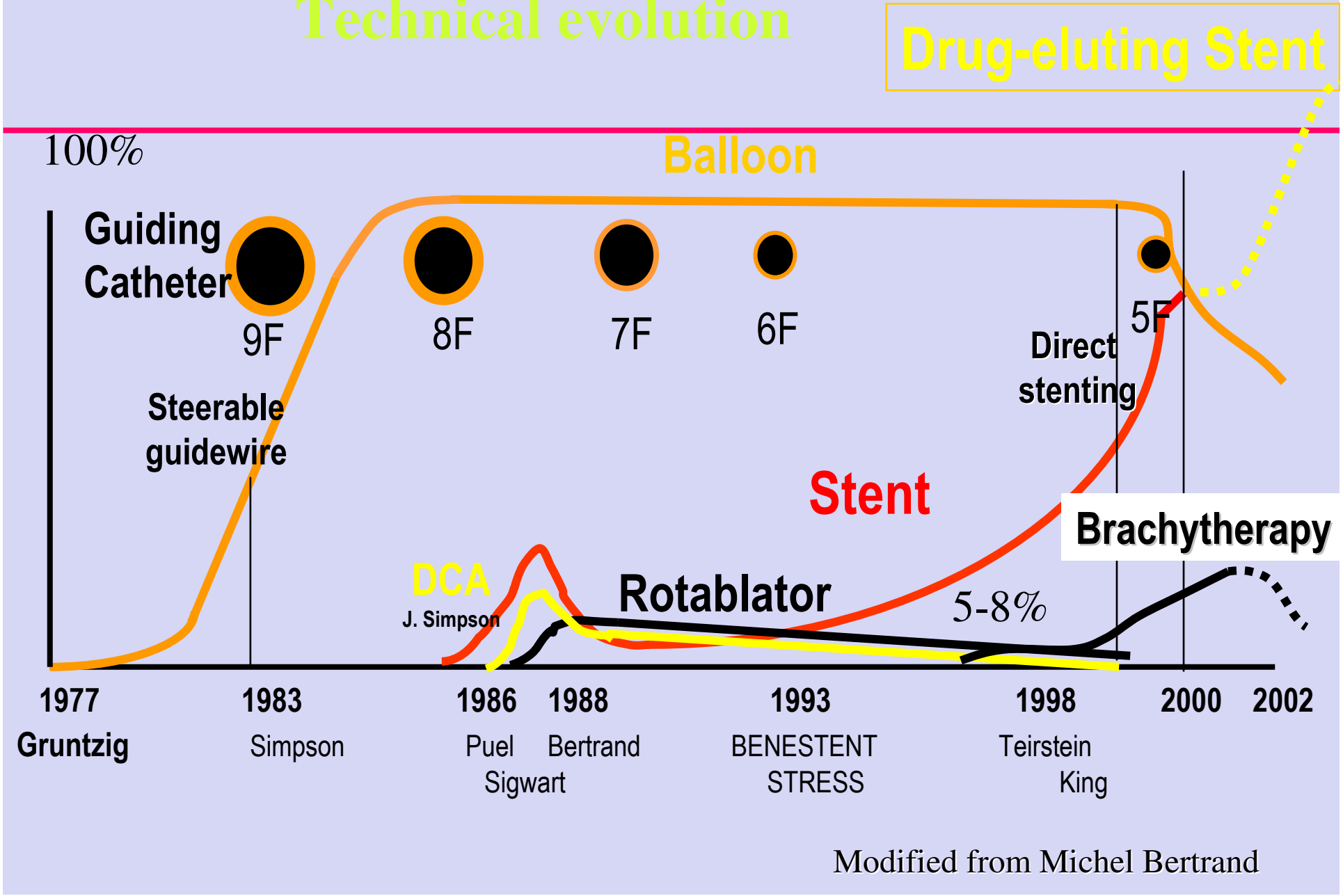
- Better Stent Designs
- Customized Stents
- Bifurcation Stents
- Coated/Covered Stents
- Radioactive Stents





Interventional Cardiology

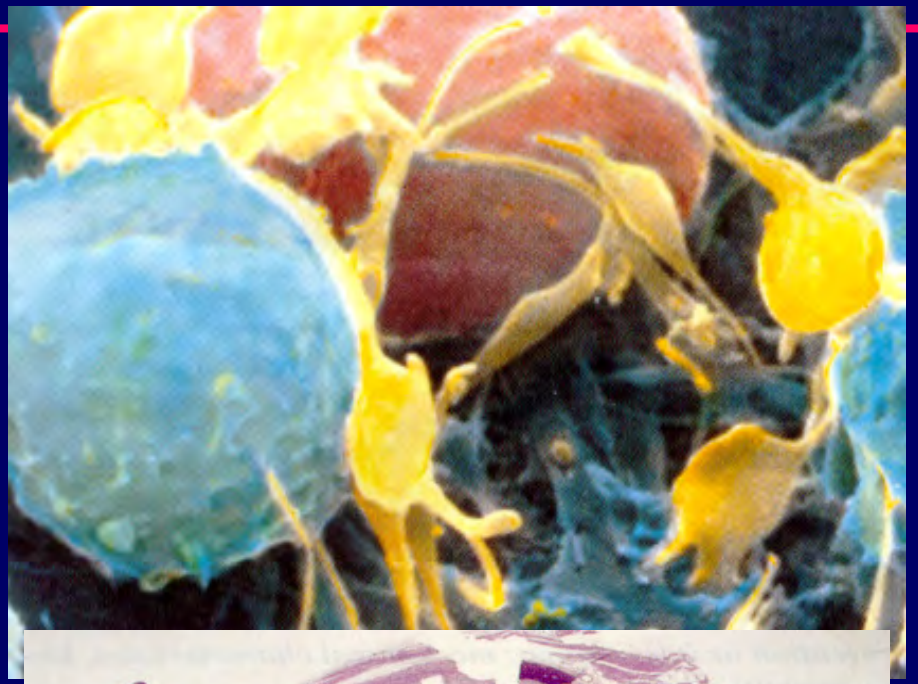
Technical evolution



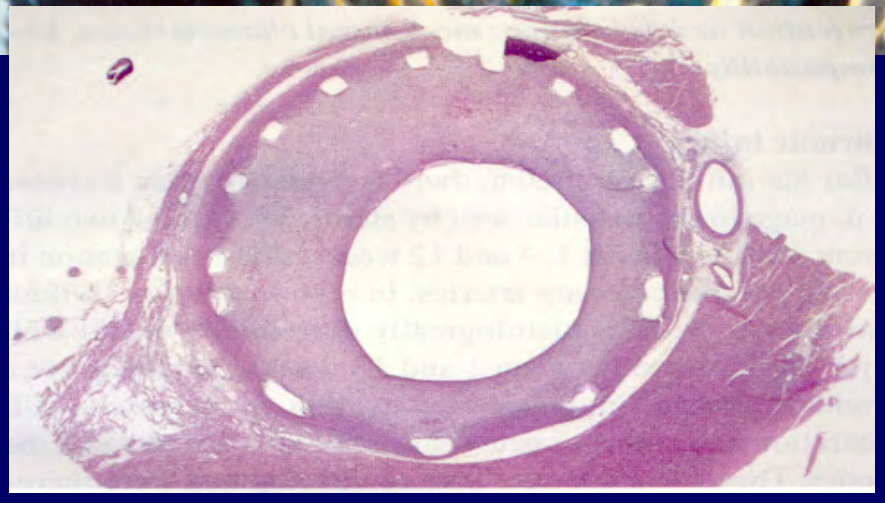
Modified from Michel Bertrand

Current Problems

- **Platelet Activation**



- **Restenosis**

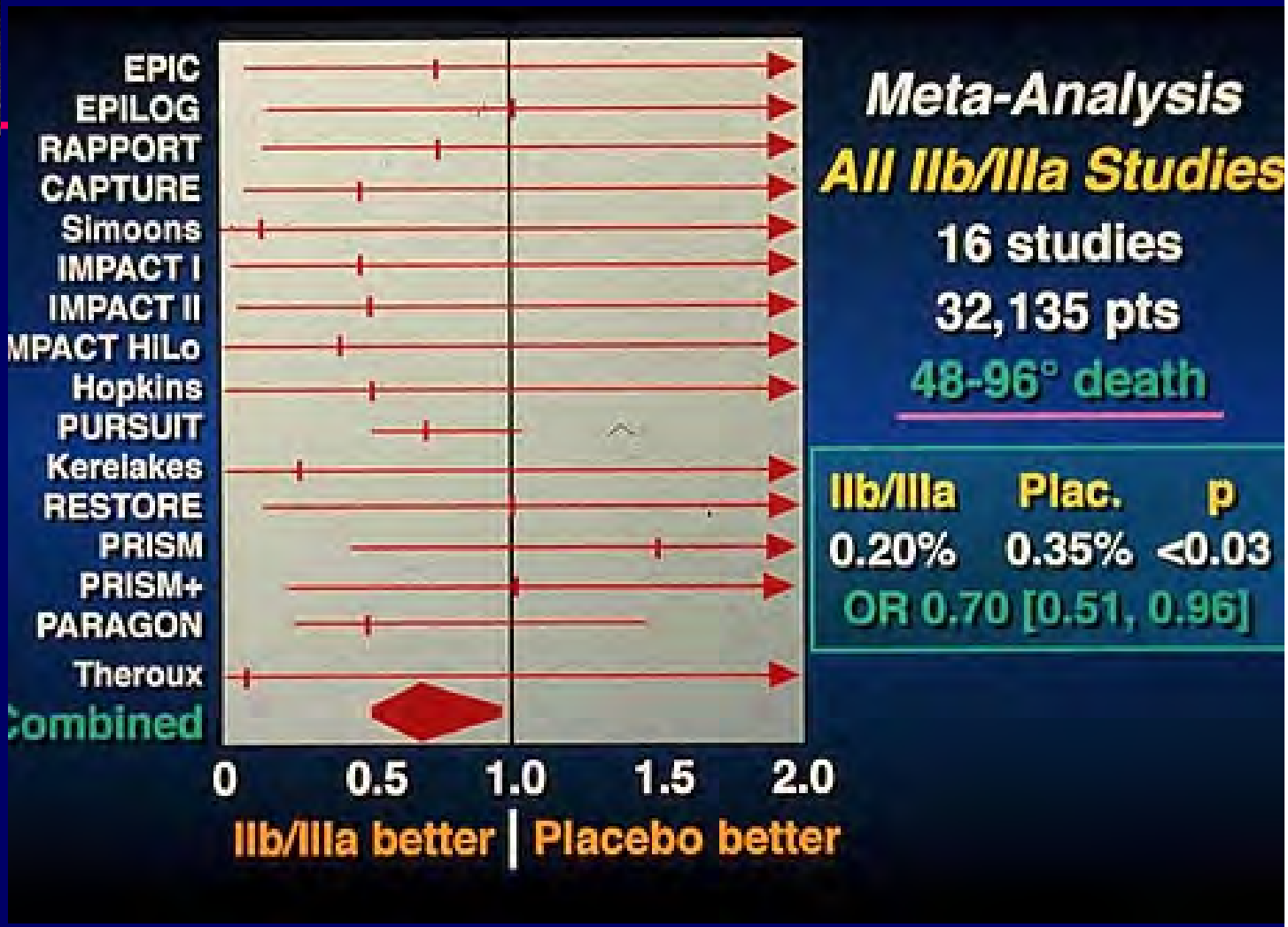


Restenosis – Data

*Model based on 1555 patients in C-DAC stent trials

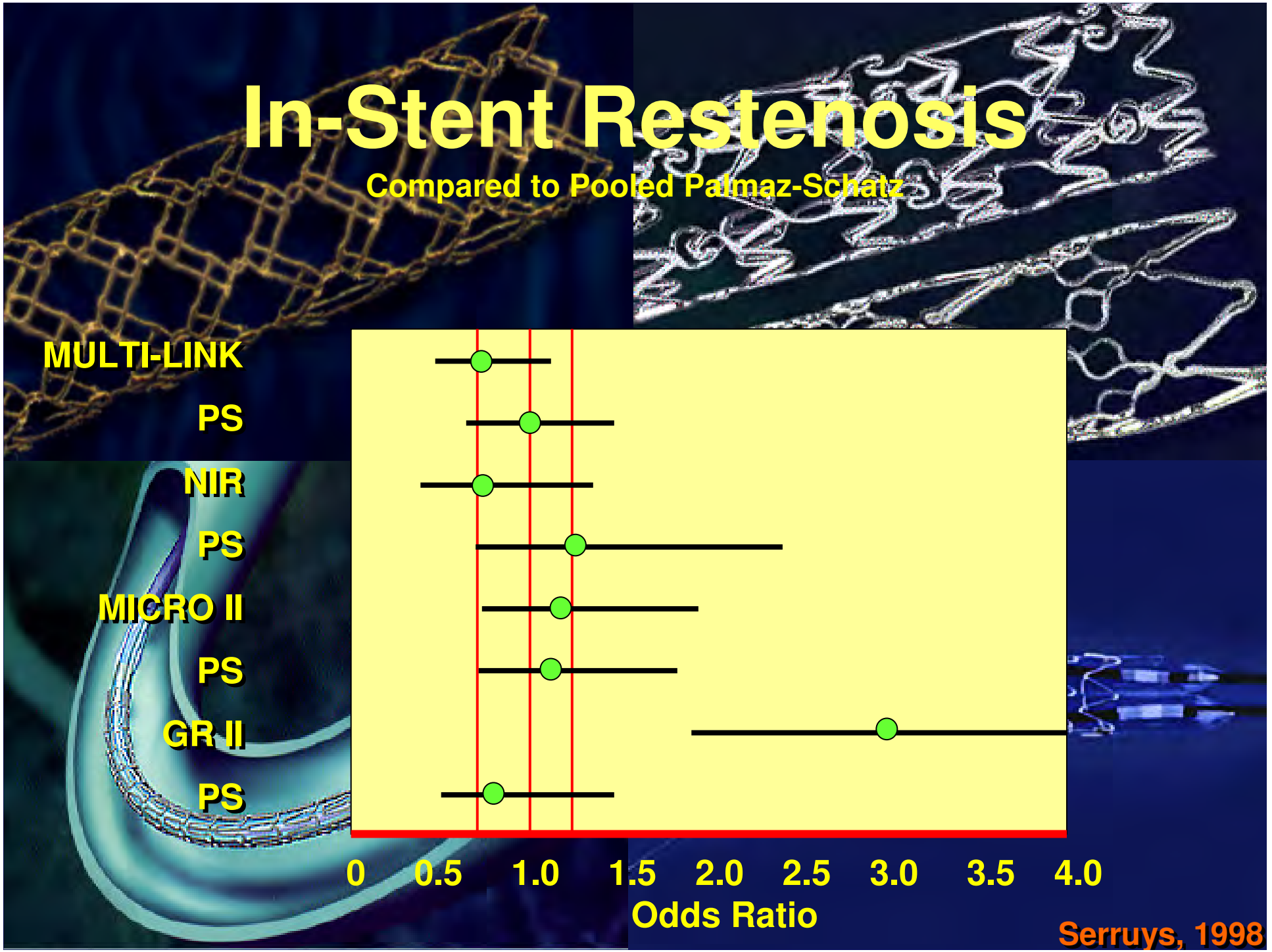
Post-Procedure In-Stent MLD	Lesion Length 10 mm	15 mm	20 mm	25 mm
Diabetics				
2.5 mm	35%	39%	43%	46%
3.0 mm	23%	26%	30%	33%
3.5 mm	15%	17%	19%	22%
4.0 mm	9%	10%	12%	14%
Non-Diabetics				
2.5 mm	27%	30%	33%	37%
3.0 mm	17%	19%	22%	25%
3.5 mm	10%	12%	14%	16%
4.0 mm	6%	7%	8%	10%


You Dummy...
The platelet was the culprit all along!


EPIC
EPILOG
RAPPORT
CAPTURE
Simoons
IMPACT I
IMPACT II
MPACT HILo
Hopkins
PURSUIT
Kereiakes
RESTORE
PRISM
PRISM+
PARAGON
Theroux
Combined
0
0.5
1.0
1.5
2.0
IIb/IIIa better
Placebo better
Meta-Analysis
All IIb/IIIa Studies
16 studies
32,135 pts
48-96° death
IIb/IIIa
Plac.
p
0.20%
0.35%
<0.03
OR 0.70 [0.51, 0.96]

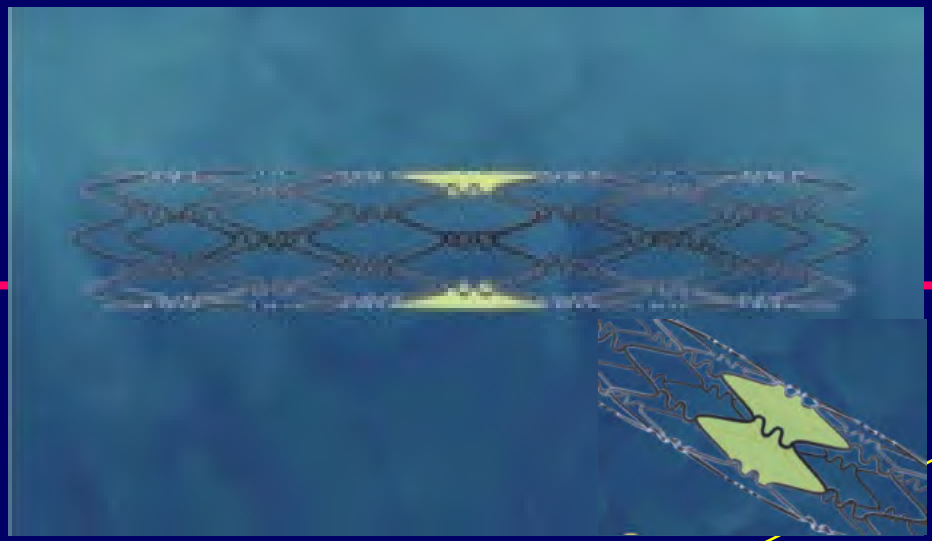
In-Stent Restenosis

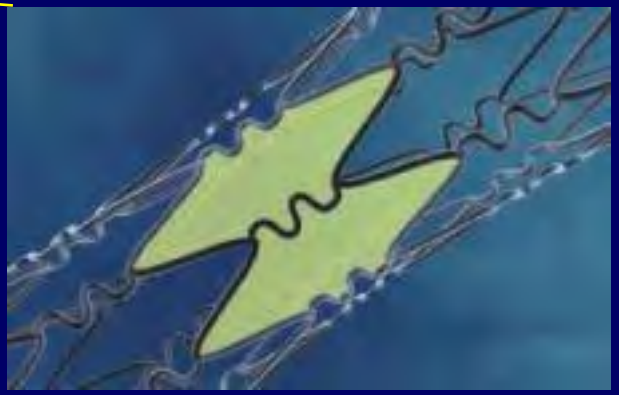
Compared to Pooled Palmaz-Schatz



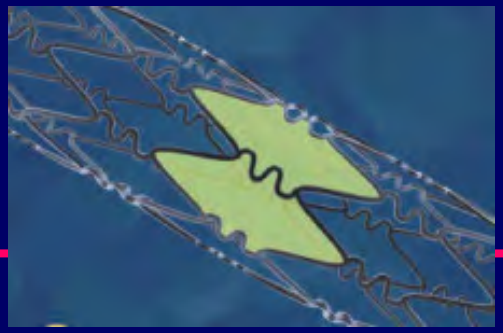
Serruys, 1998

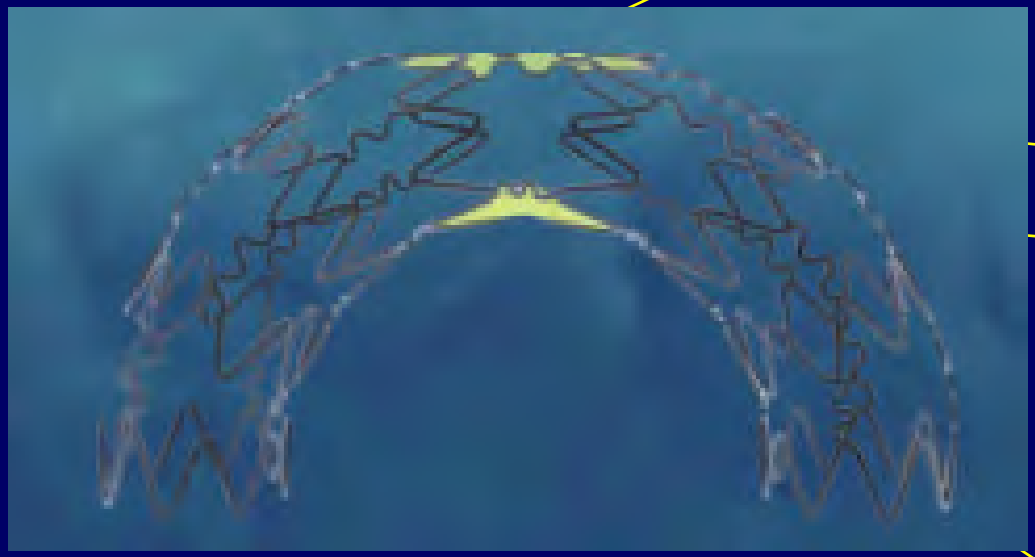
Closed Cell Design



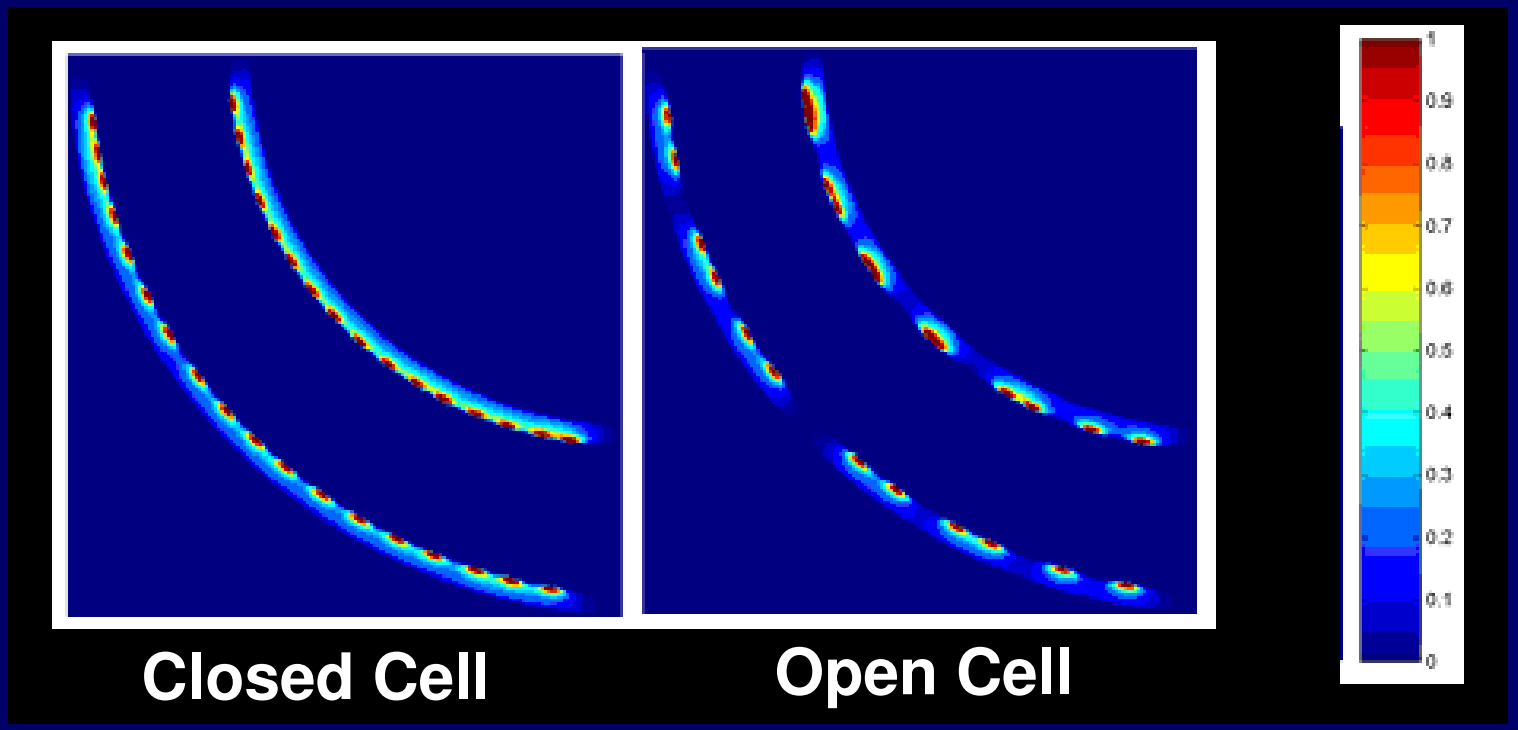


Open Cell Design





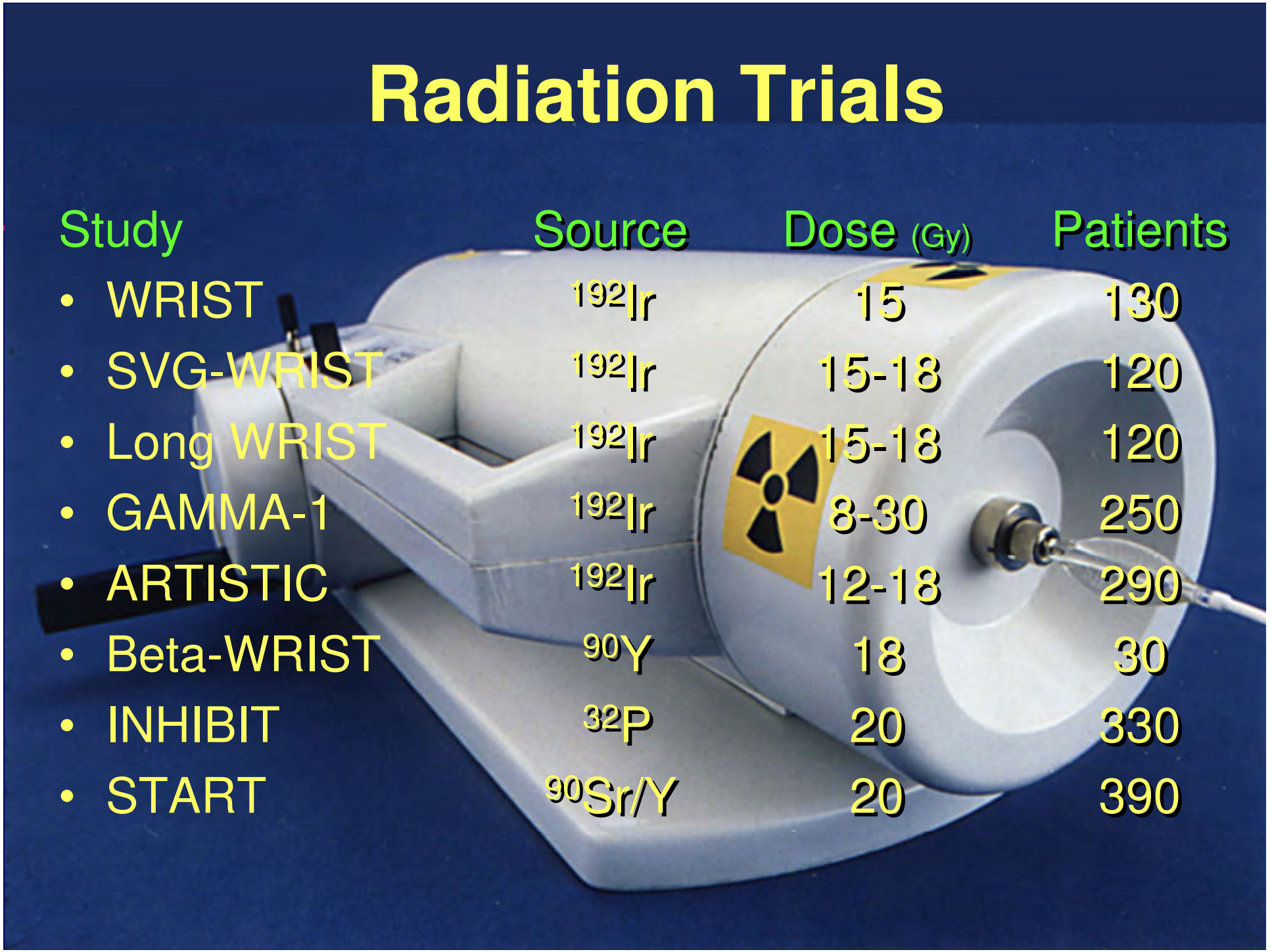
Closed Cell vs Open Cell Stents



Pharmacological approches to prevent restenosis

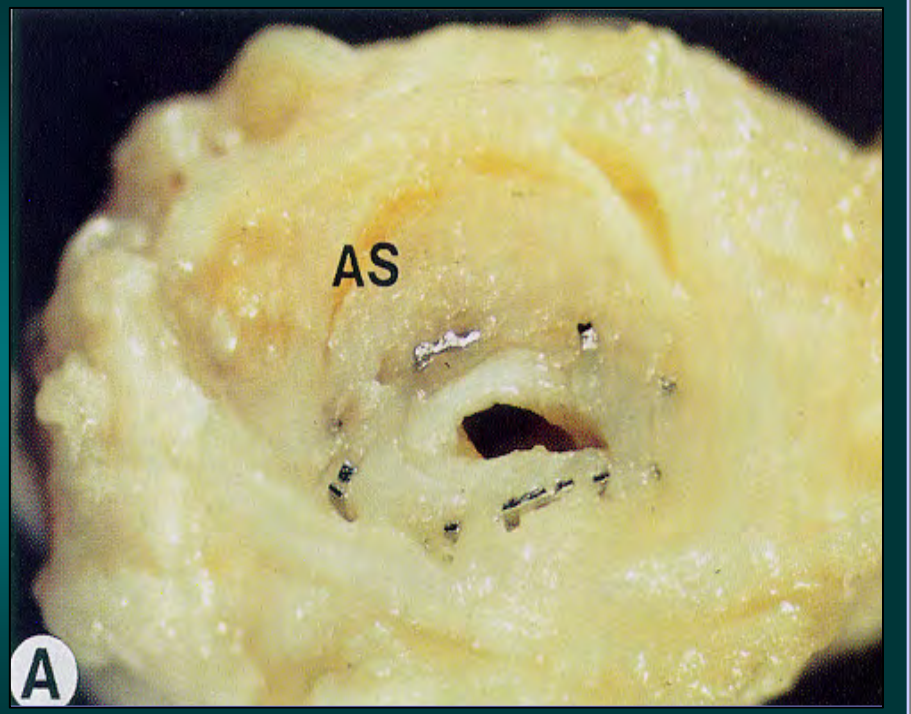
- Antiplatelet and antithrombotic agents
- Anti-inflammatory drugs
- Specific growth factor antagonist
- Antiproliferatives and antineoplastics
- Vasodilators
- Lipid-lowering agents and antioxidants
- Local drug delivery and molecular strategies

Radiation Trials



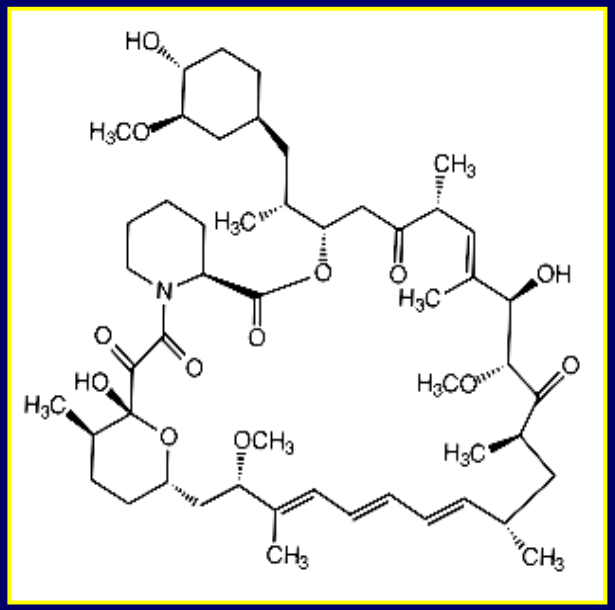
Study	Source	Dose (Gy)	Patients
• WRIST	^{192}Ir	15	130
• SVG-WRIST	^{192}Ir	15-18	120
• Long WRIST	^{192}Ir	15-18	120
• GAMMA-1	^{192}Ir	8-30	250
• ARTISTIC	^{192}Ir	12-18	290
• Beta-WRIST	^{90}Y	18	30
• INHIBIT	^{32}P	20	330
• START	^{90}Sr/Y	20	390

In-Stent Restenosis



Sirolimus (Rapamycin)

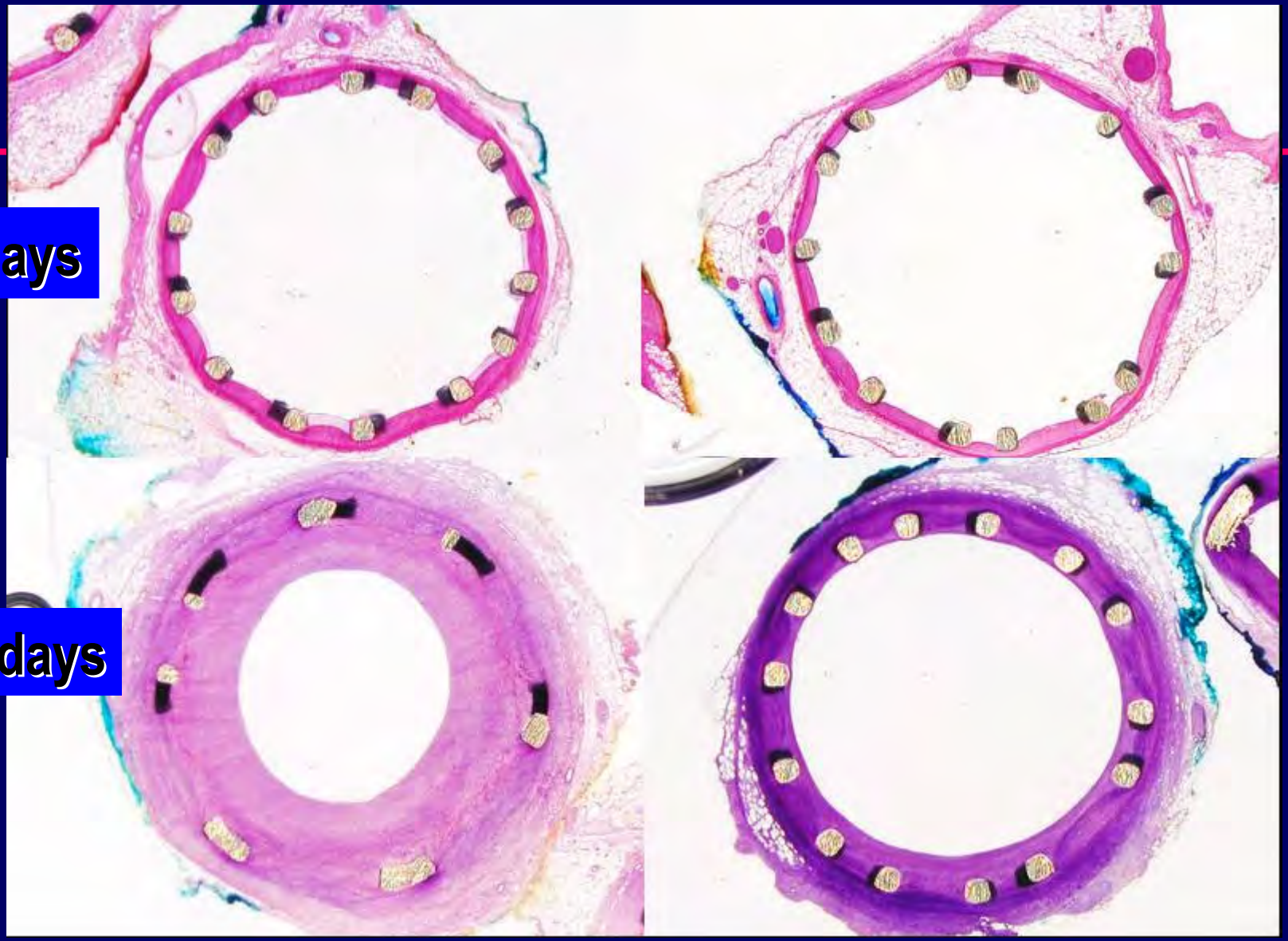
- A naturally occurring antimicrobial first found on Easter Island
- Potent immunosuppressive activity
- Developed and marketed by Wyeth Ayerst Labs for prevention of renal transplant rejection (Rapamune®)*
- Novel inhibitor of growth factor & cytokine-stimulated cell proliferation
- Mechanism of action: cell-cycle inhibition



Sirolimus, mw = 914

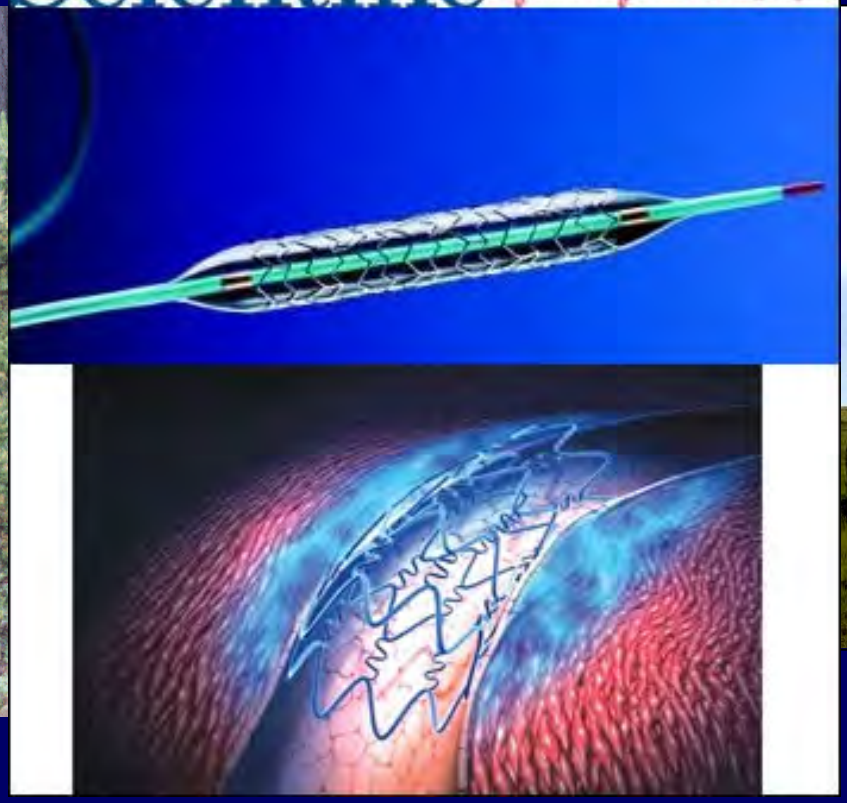
*Rapamune is a registered trademark of Wyeth Ayerst.

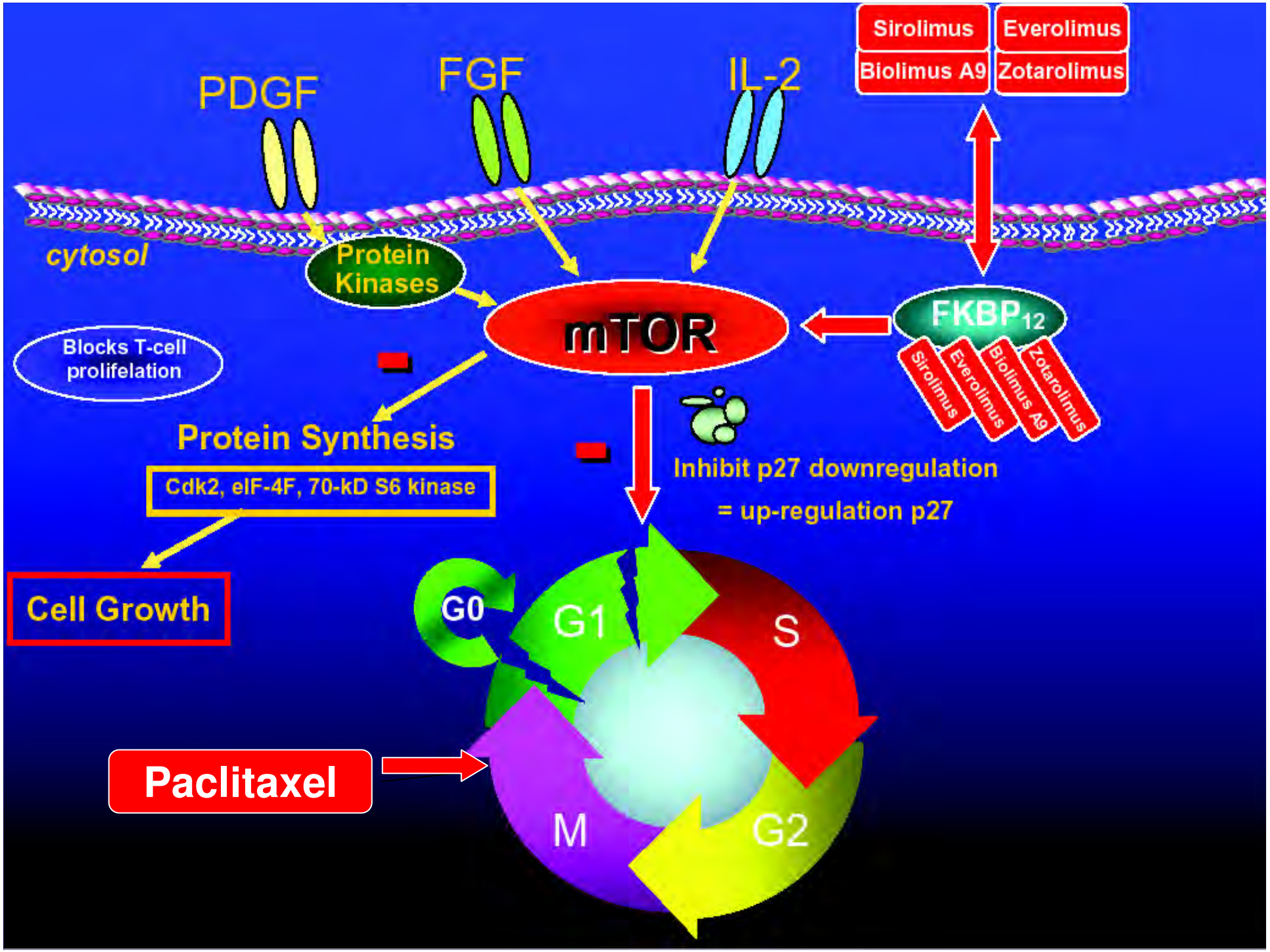
Histology of Sirolimus stent



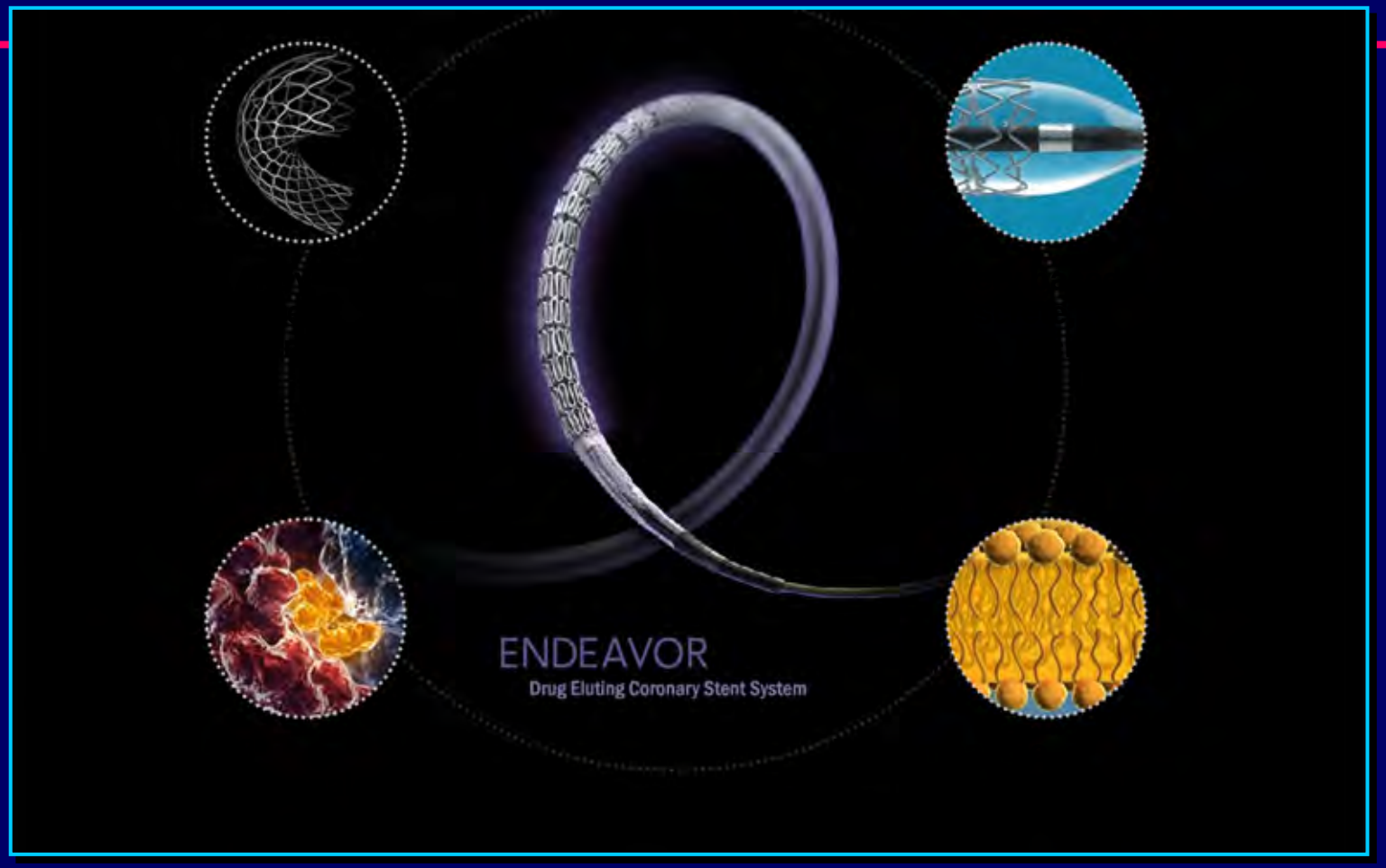
The DES Revolution

Boston Scientific Cordis
a Johnson-Johnson company




Sirolimus
Everolimus
Biolimus A9
Zotarolimus
PDGF
FGF
IL-2
cytosol
Protein Kinases
mTOR
FKBP12
Sirolimus
Everolimus
Biolimus A9
Zotarolimus
Blocks T-cell prolifelation
Protein Synthesis
Cdk2, eIF-4F, 70-kD S6 kinase
Inhibit p27 downregulation
= up-regulation p27
Cell Growth
G0
G1
S
M
G2
Paclitaxel

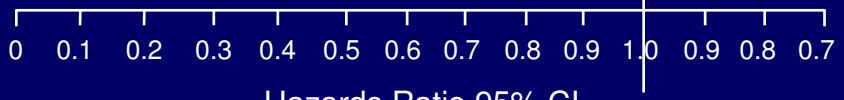
Components of the Endeavor Stent



SIRIUS Clinical Data:

Odds Ratio for TLR by Subgroup at 9 Months

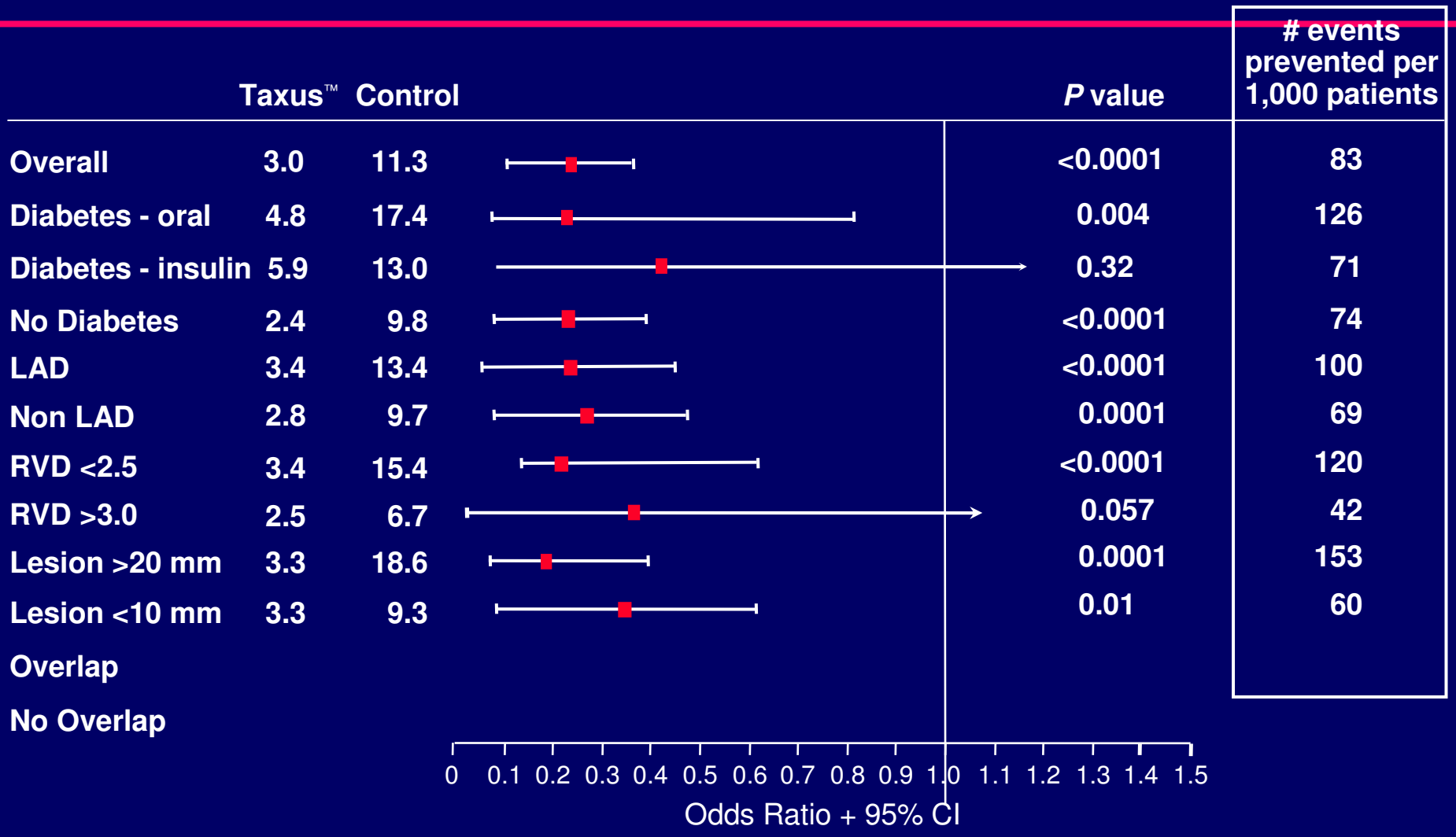
	Sirolimus	Control	*P* value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



E. Perin, Challenging Decisions in the Use of Drug-Eluting Stents, The Journal of Invasive Cardiology, Volume 16/Supplement F, Sept 2004

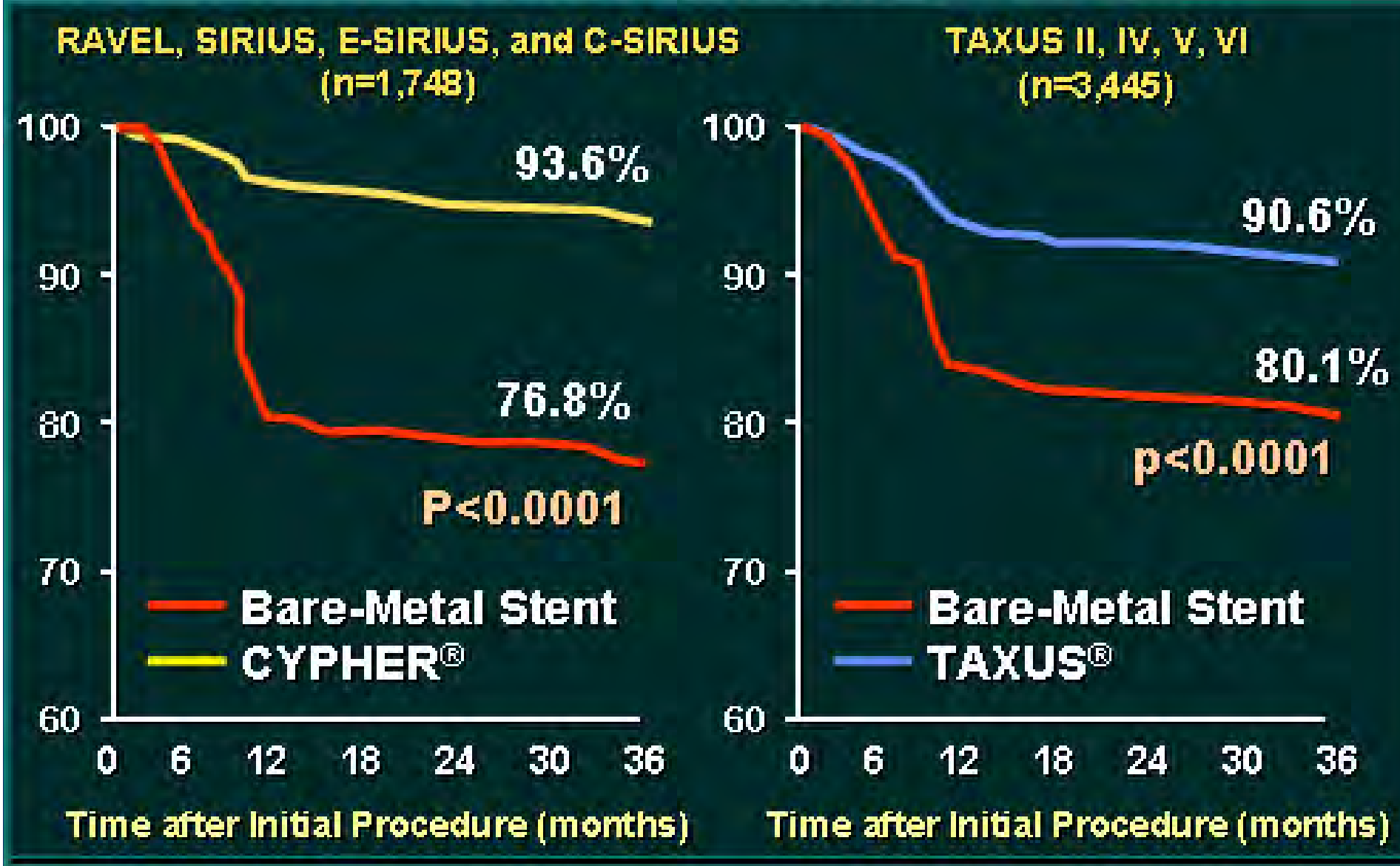
TAXUS IV Clinical Data:

Odds Ratio for TLR by Subgroup at 9 Months



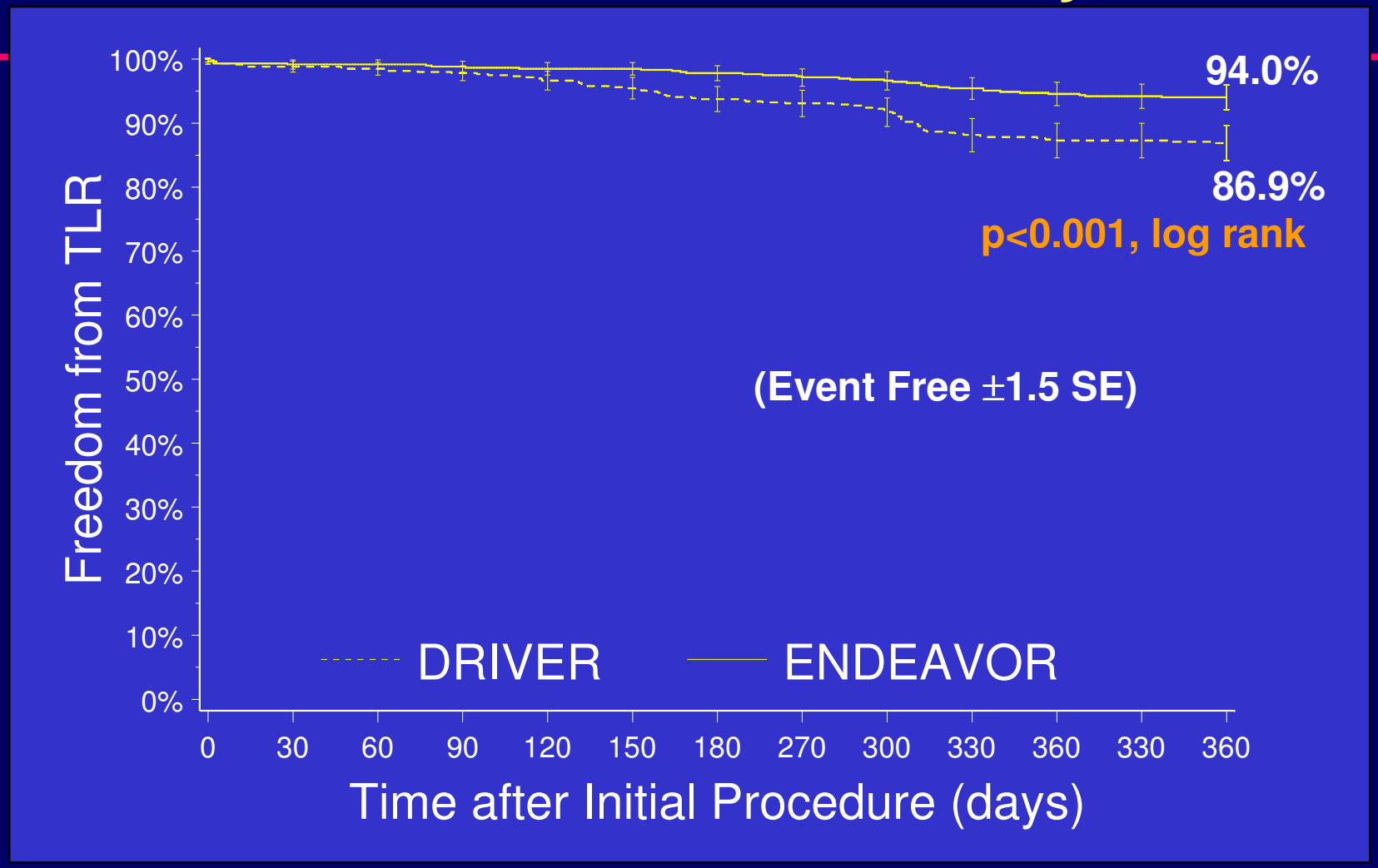
E. Perin, Challenging Decisions in the Use of Drug-Eluting Stents, The Journal of Invasive Cardiology, Volume 16/Supplement F, Sept 2004

Freedom from TLR

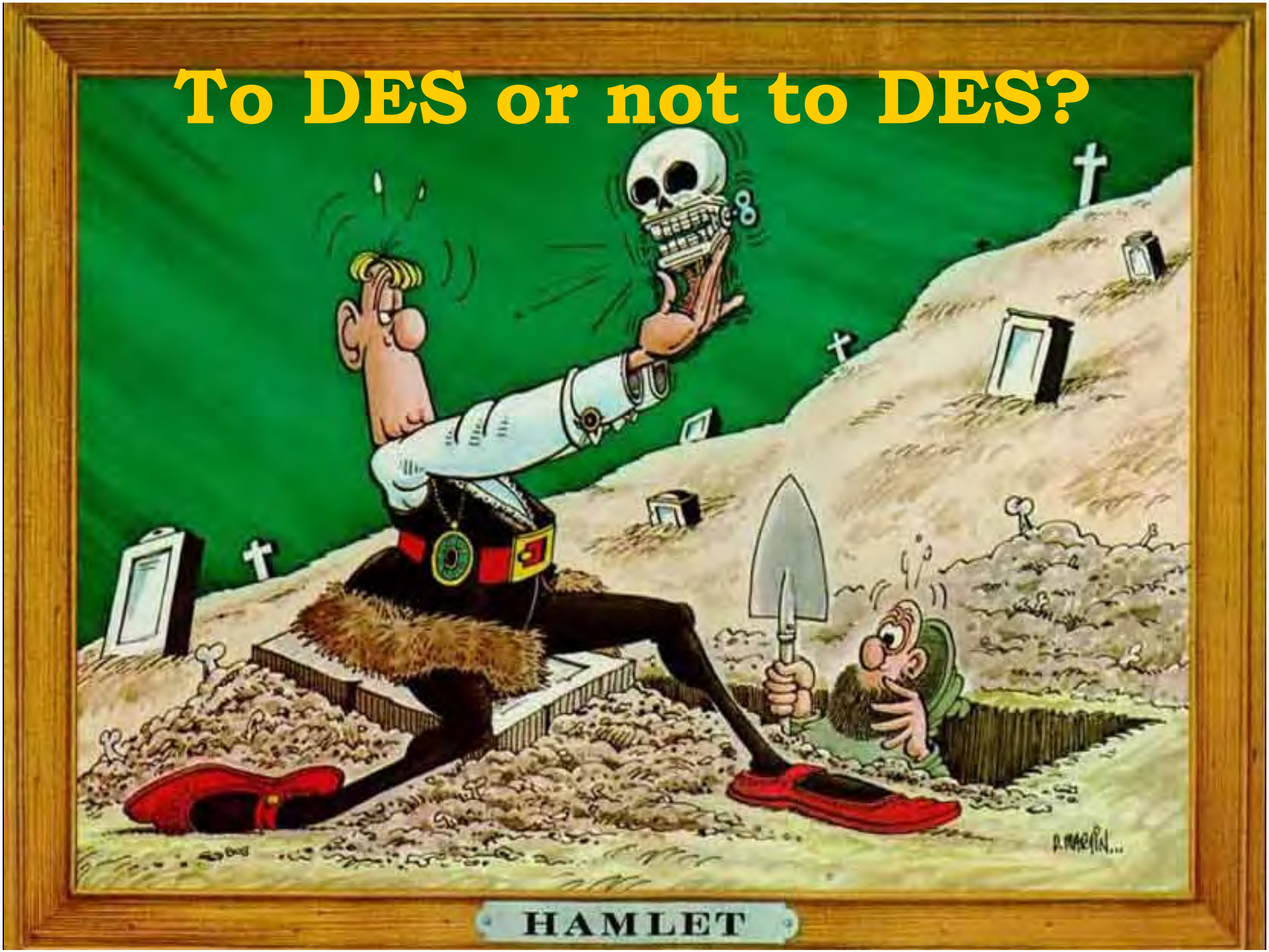


ENDEAVOR II

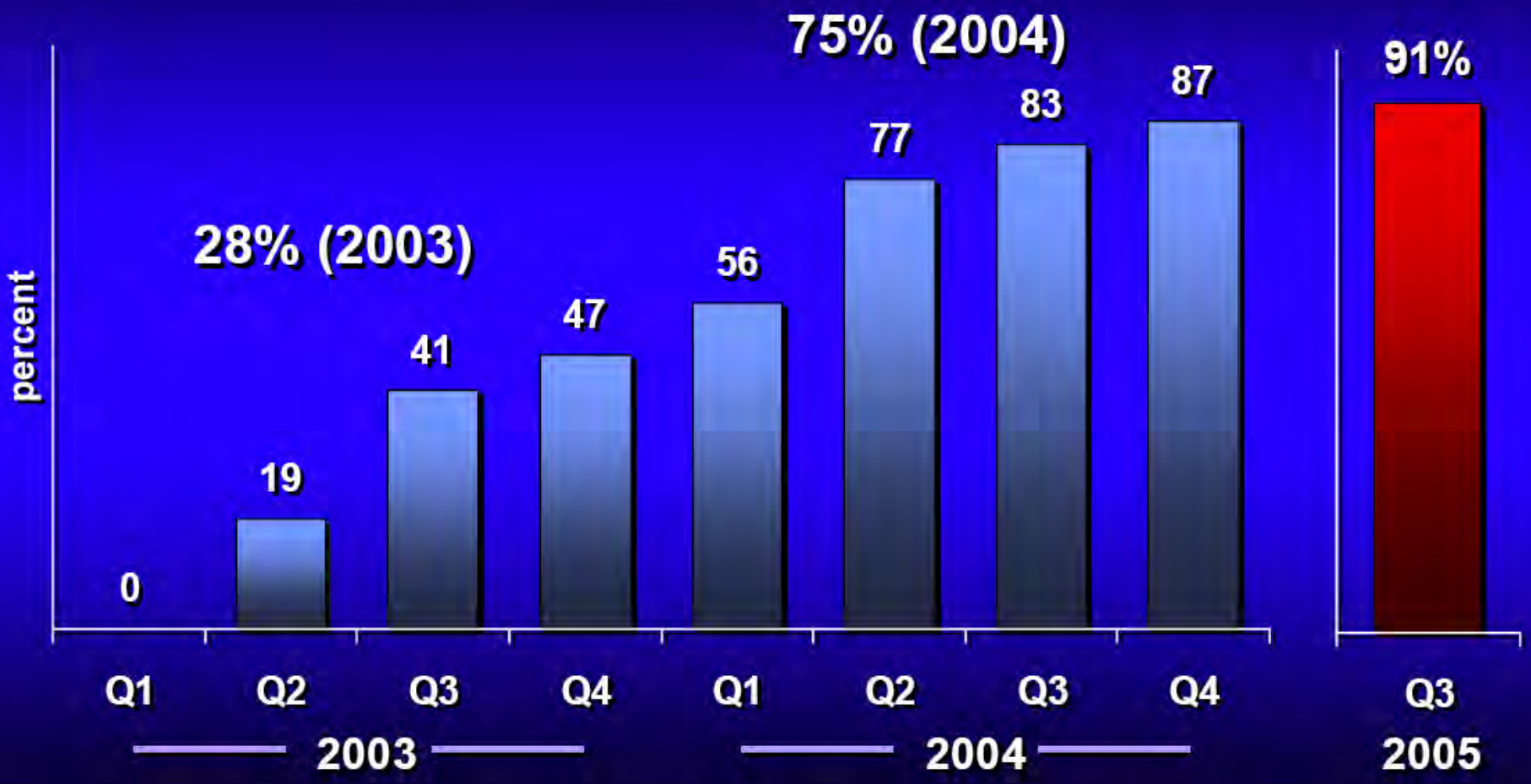
TLR-Free Survival at 360 Days



To DES or not to DES?

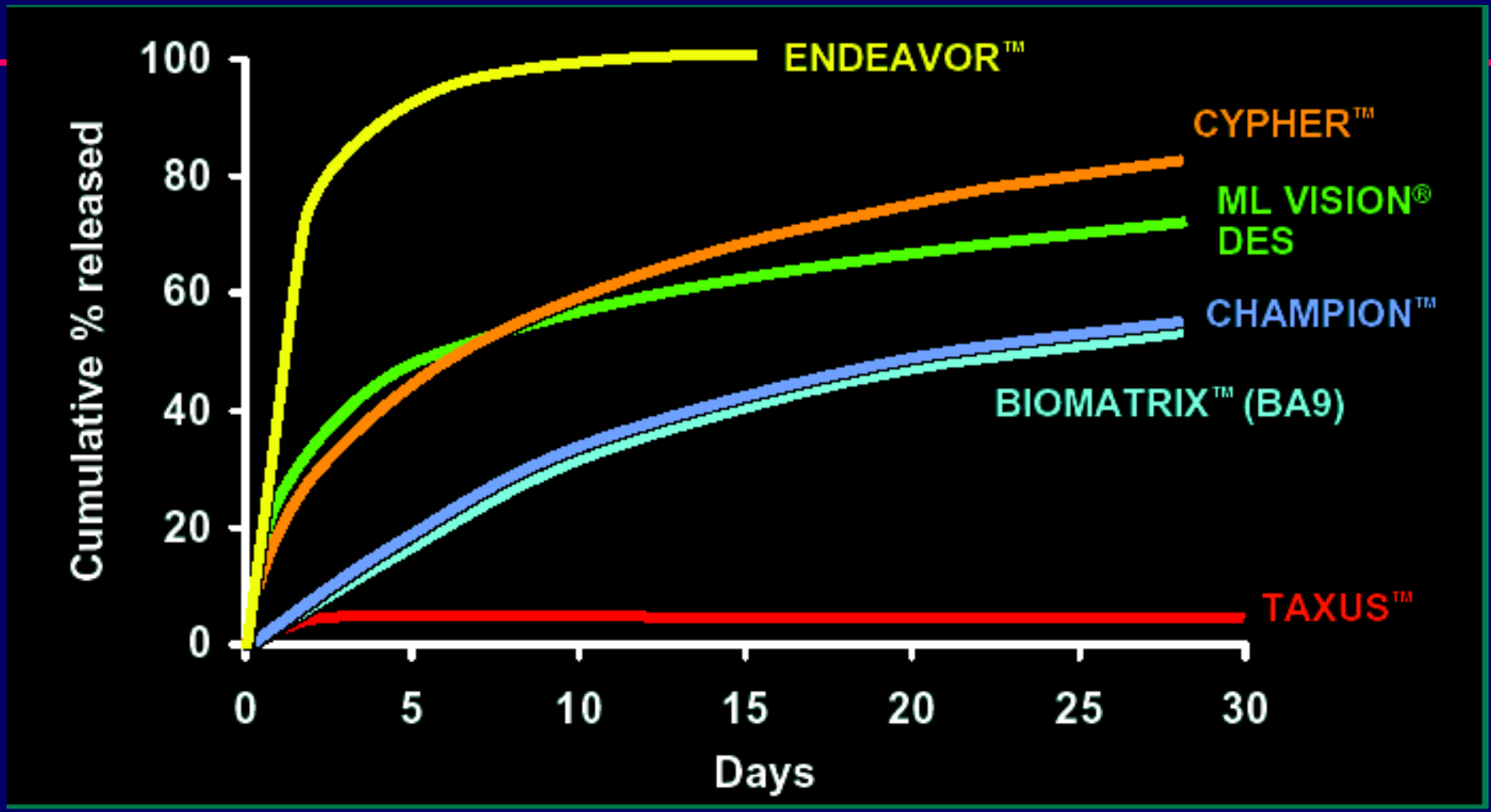


DES Penetration in the United States: Dominant Technology

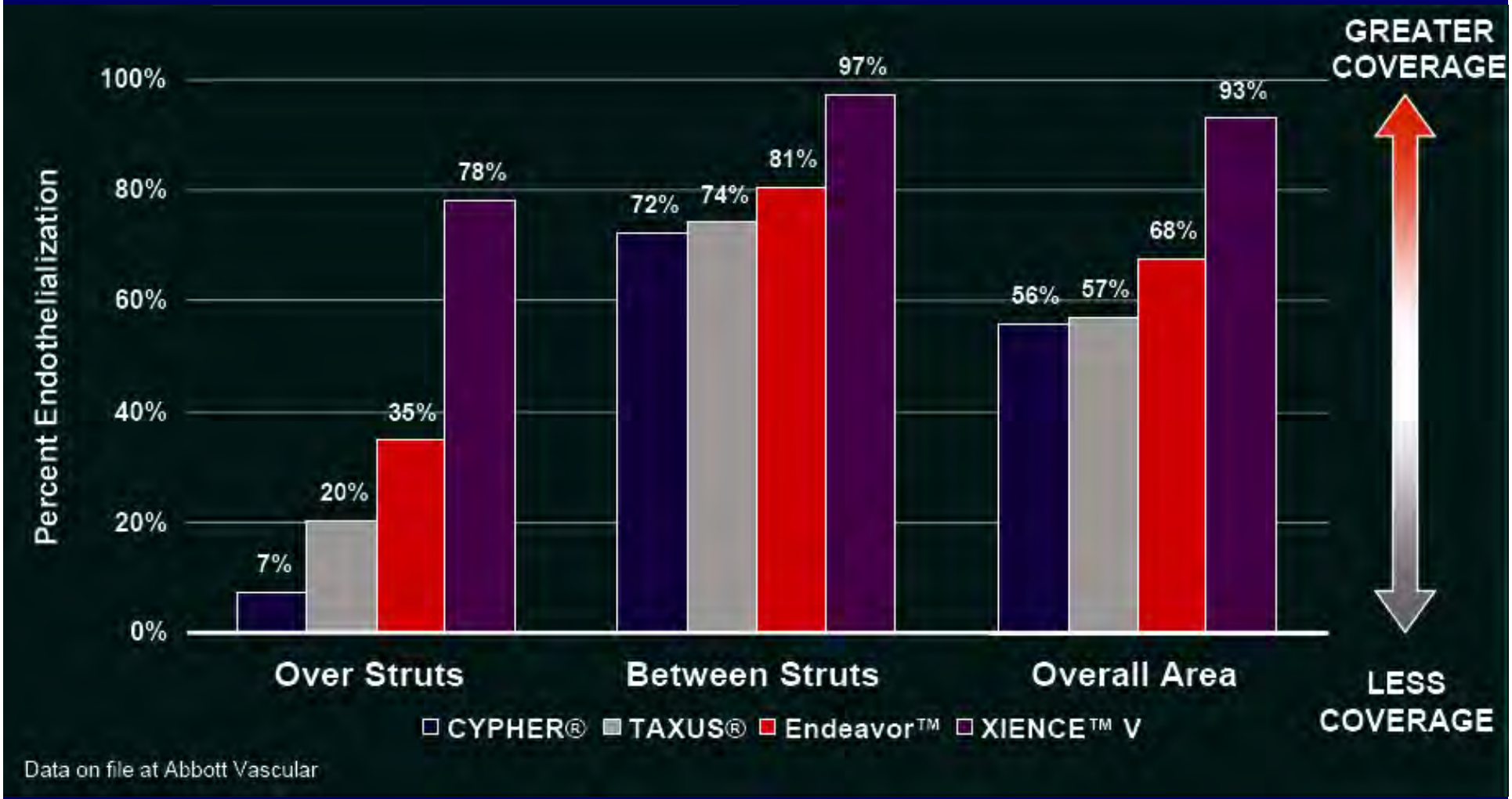


Cypher approved April 2003 and Taxus approved March 2004

Choice of DES: Release Kinetics

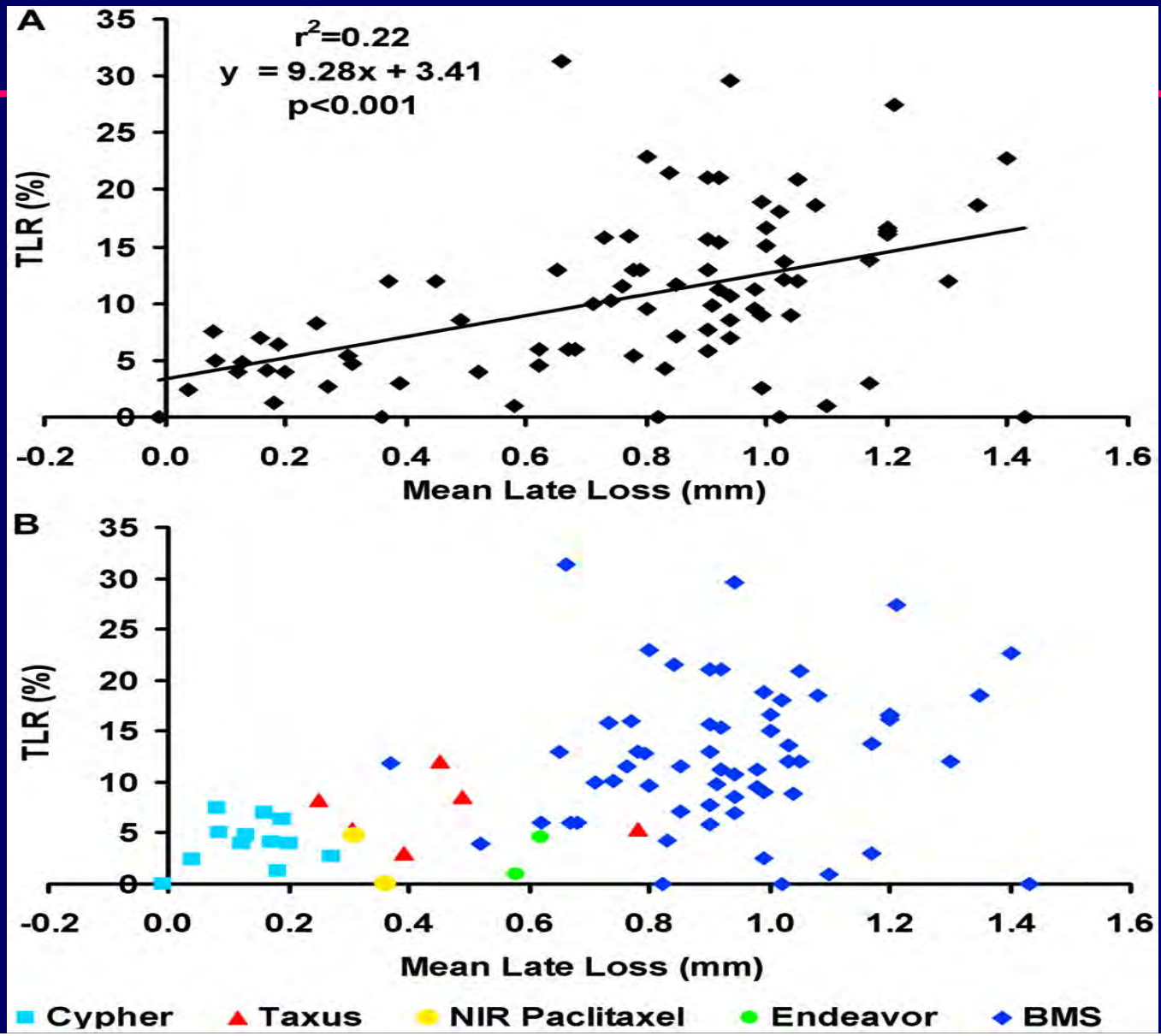


Stent Re-endothelialization @ 14 d.
Rabbit Iliac



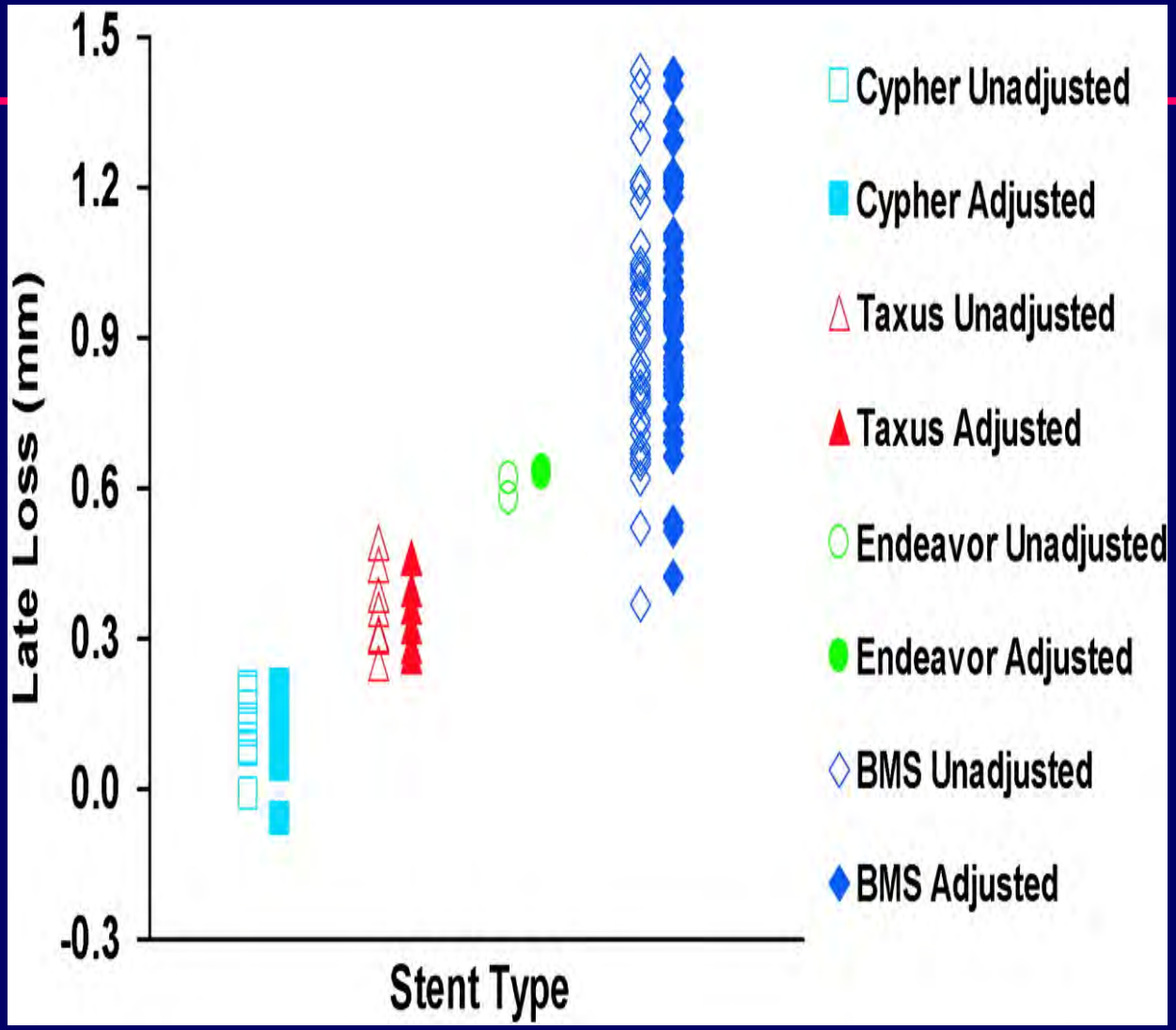
Data on file at Abbott Vascular

Late Loss & TLR Vs. Stent Type



Mauri et al.
Circ 2005

Late Loss and stent type



t al. Circulation 2005

Adjusted to DM and lesion length

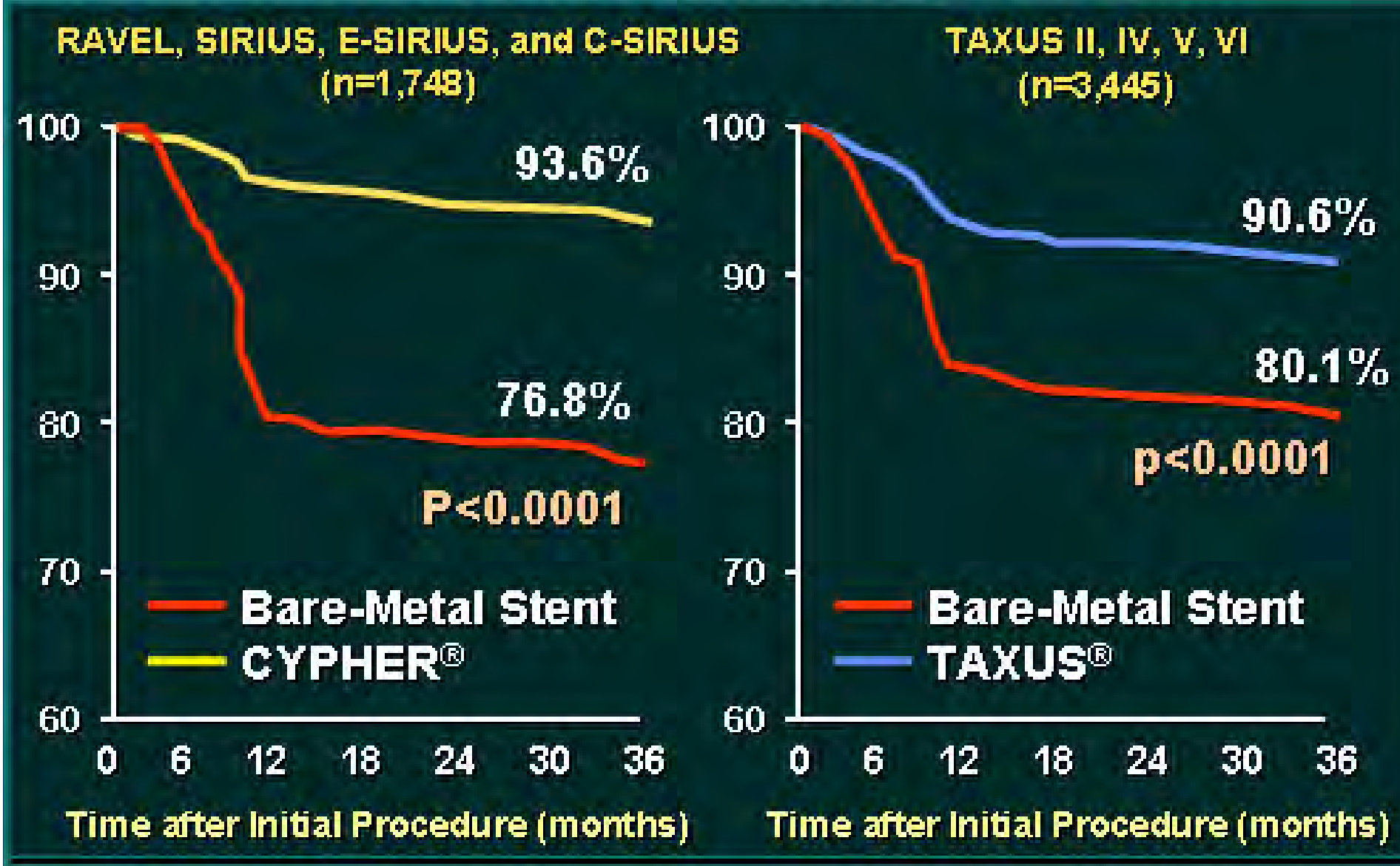
Choice of Stent

CYPHER Sirolimus-eluting Stent	TAXUS paclitaxel-eluting stent	ENDEAVOR ABT-578 eluting Stent
140 µg/cm^2 sirolimus	100 µg/cm^2 paclitaxel	ABT-578
Cytostatic MoA antiproliferative and anti-inflammatory action	Cytotoxic MoA antiproliferative effect	Sirolimus analogue
Released from closed-cell stent system	Closed-cell stent system	Open cell system

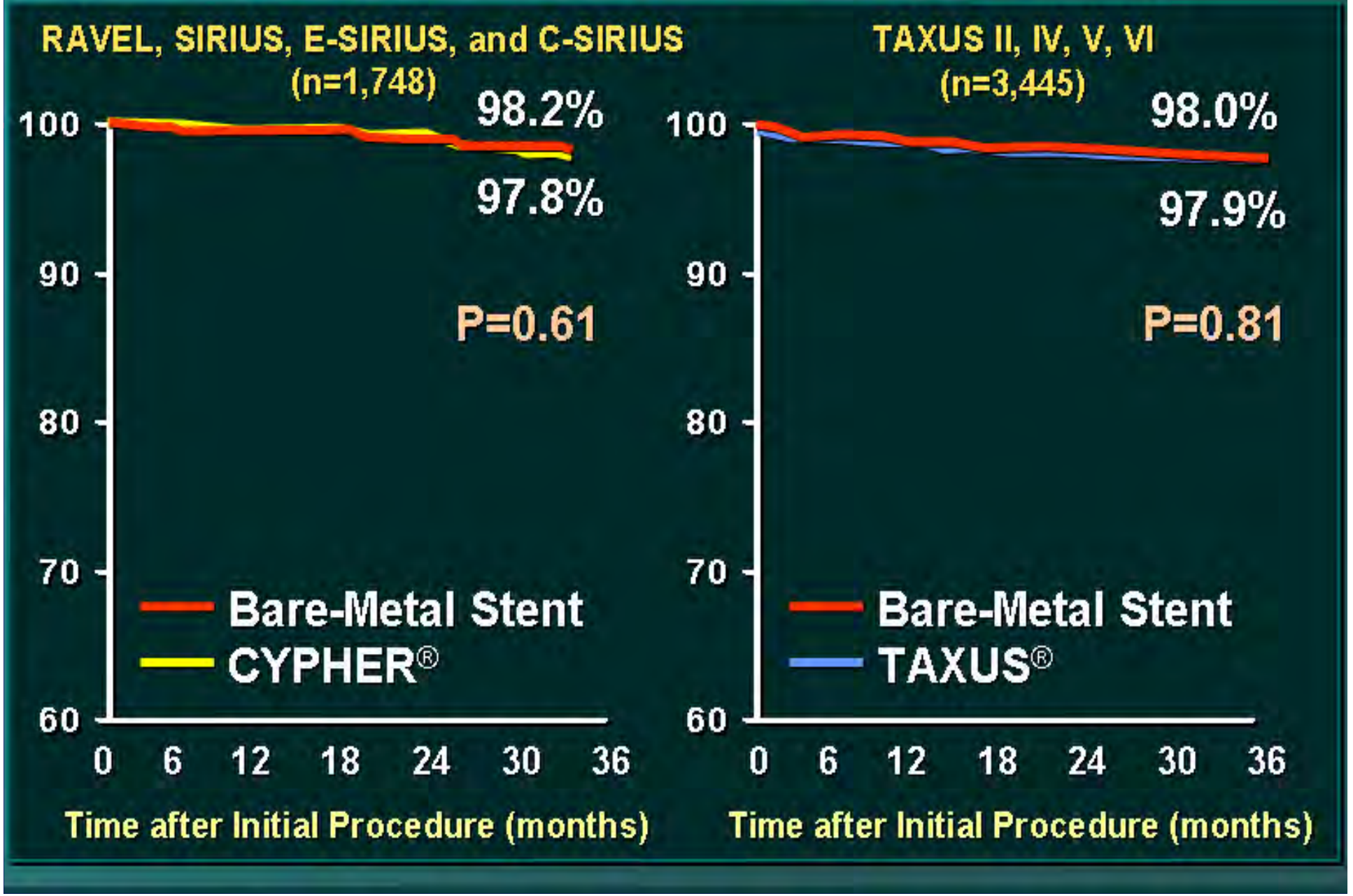
RCTs Comparing Cypher to Taxus

	TAXi	REALITY	SIRTAX	ISAR-Diabetes
Study design	not defined	Cypher superior	Cypher superior	non-inferior
Multicenter	no	yes	no	no
Clininical primary endpoint	n/a	no	yes	no
Primary endpoint	n/a	angiographic	clinical	angiographic
Time of PE	6 months	8 months	9 months	6 months
Parameter	n/a	in lesion RR	MACE	in-segment LLL
Patients	102/100	684/669	503/509	125/125
Lesion length	not mentioned	(17.0/17.3)10<;15<	"all"(12.4/13.4)	13.8/12.4
Vessel diameter	(3.2/3.2)	(2.4/2.4)3.0–2.25	(2.8/2.8)4.0–2.25	2.7/2.8
Restenosis in Segment	n/a	9.6/11.1	*6.7/11.9	*6.9/16.5
Late lumen Loss in Stent	n/a	*0.09/0.31	*0.13/0.25	*0.43/0.67
TVR	2.0/1.0	1.6/1.2	*6.0/9.2	6.4/12.2TLR
MACE	6.0/4.0	9.2/10.8	*6.2/10.8	
Primary Endpoint reached	n/a	no	yes	No; in Seg LL(0.19/0.46*)
Major limitation	no primary endpoint	no clinical primary endpoint	no multicenter trial	no clinical primary endpoint
The only study reaching the primary endpoint was SIRTAX, but it was not a multicenter study. There is no randomized, controlled multicenter trial with a primary clinical endpoint and adequate power showing that one DES is superior to another.				

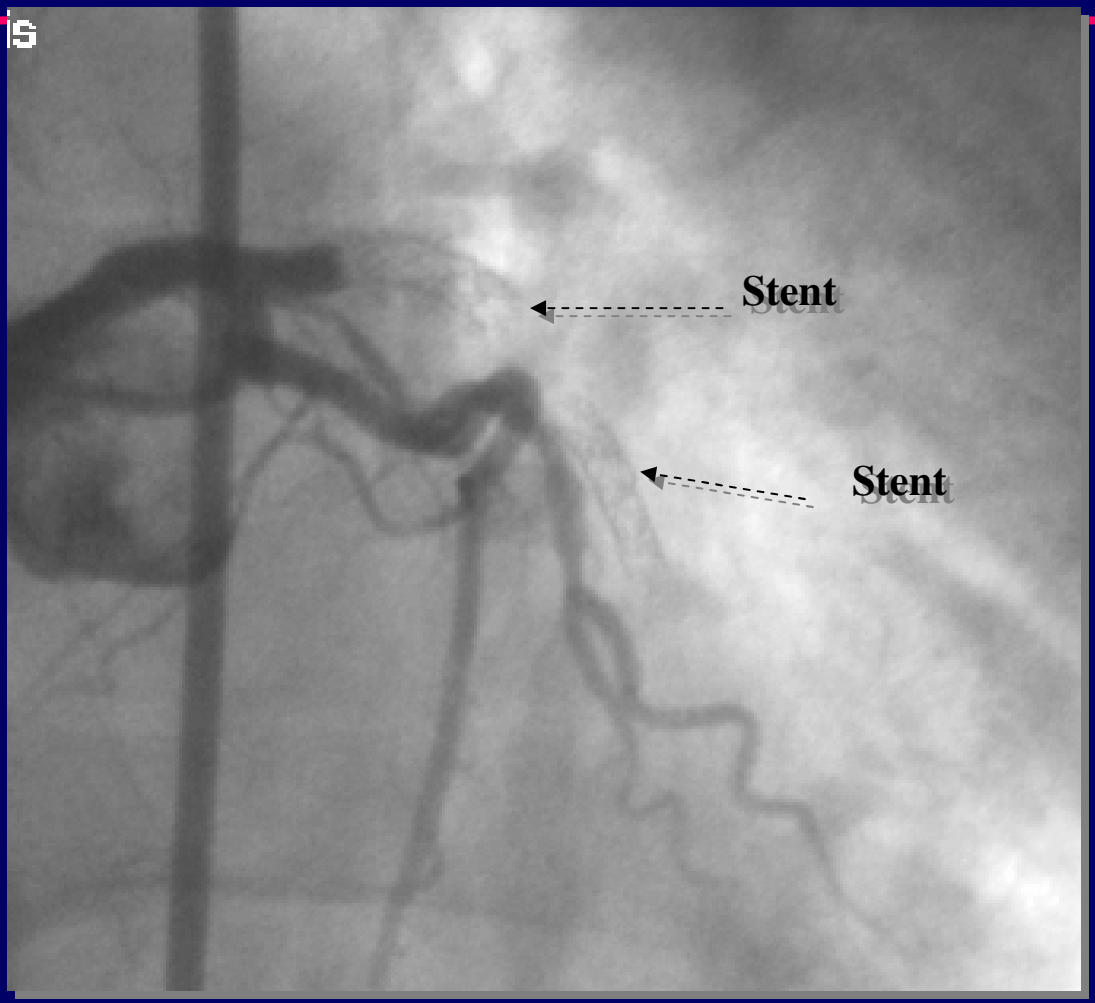
Freedom from TLR



Freedom from Cardiac Death

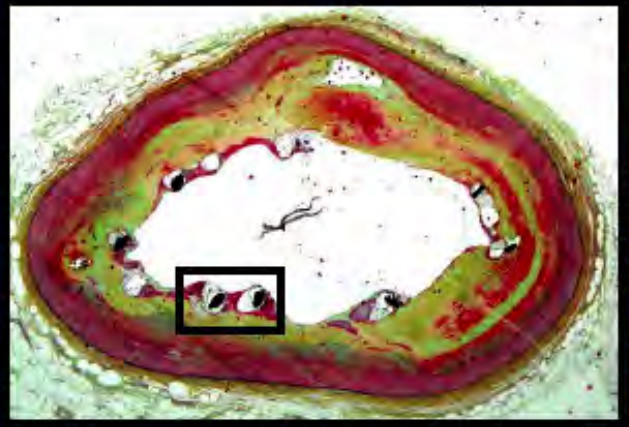


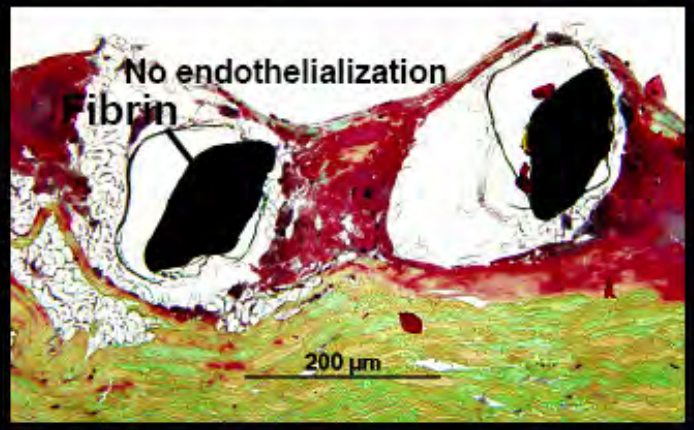
STENT THROMBOSIS



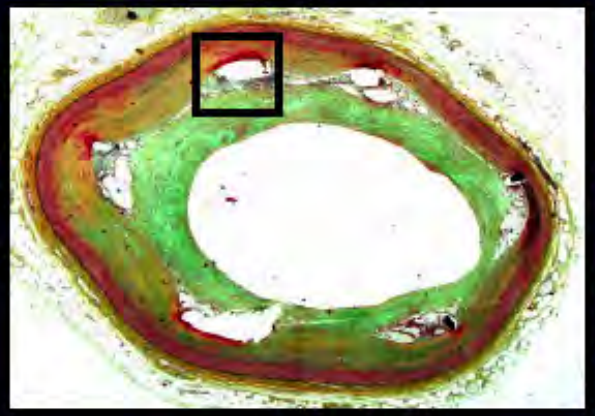
Bare Metal Stent in Proximal RCA and SRL-Eluting Stent in Distal RCA 15 Months Antemortem (Non-Cardiac Death)

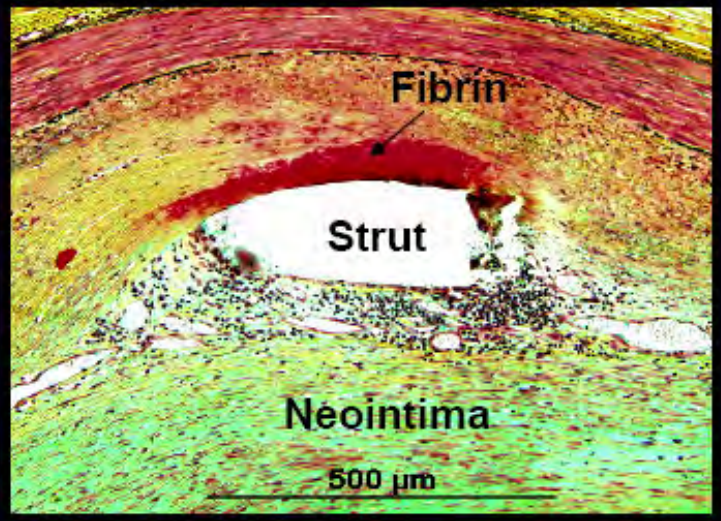
SRL-Eluting





Bare Metal Stent



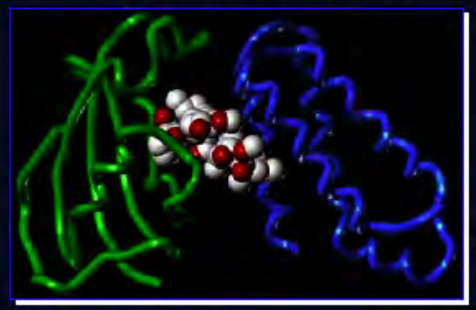


Joner M. JACC 2006;48:193–202

The Biolimus A9 Stent

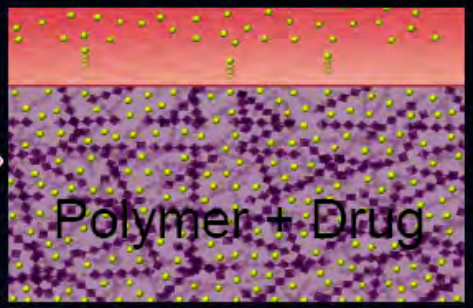
Biosensors open cell S stent

Biolimus A9



- potent
- cytostatic
- anti-prolif/inflamm

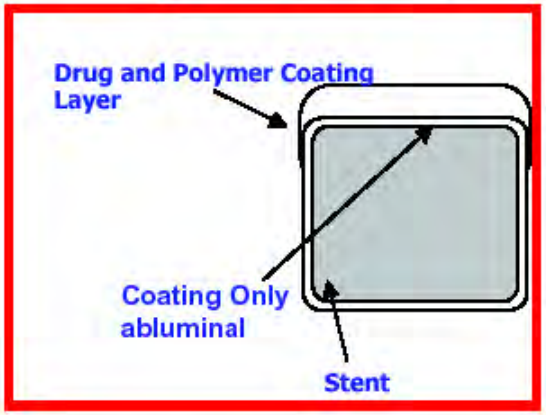
BA9 Stent



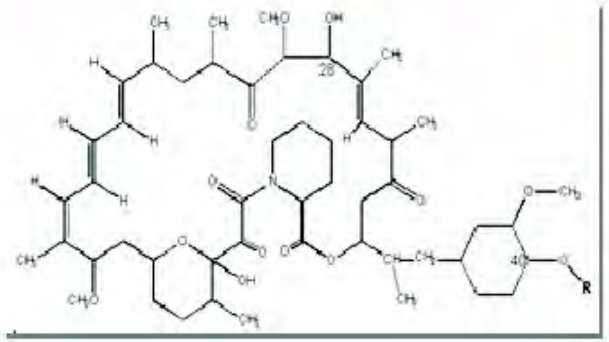
Bioabsorbable PLA polymer composite

Nobori DES Components

S-Stent™ (stainless steel)
- Quadrature-link design
- Excellent flexibility and scaffolding
- Reduced turbulence and wall injury



PLA bioabsorbable Polymer
- High drug-carrying capacity
- Controlled **biodegradability**
- Simultaneous polymer degradation and release of drug into tissue
- Abluminal Coating



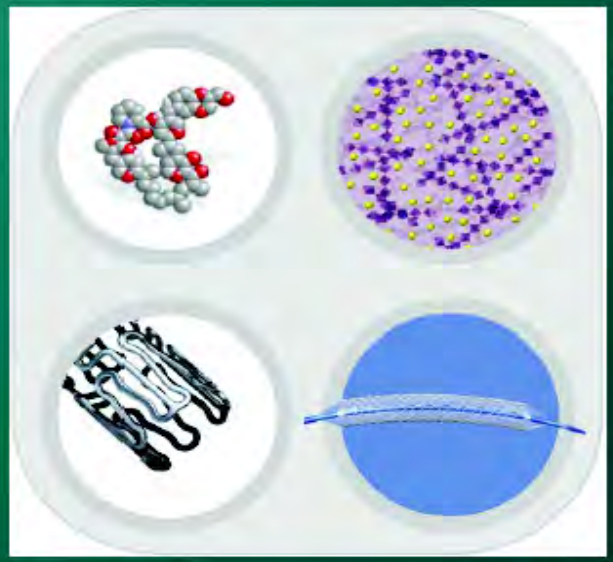
Biolimus A9™ (rapamycin derivative)
- A potent new “Limus” designed for stent applications
- Powerful immunosuppressant, anti-inflammatory compound
- Prevents smooth muscle cell proliferation
- Highly lipophylic; elutes fast from stent

New Stents:
Everolimus eluting stents

Guidant XIENCE V DES

Everolimus

ML VISION®
Stent Platform



Durable Polymer
Control Release

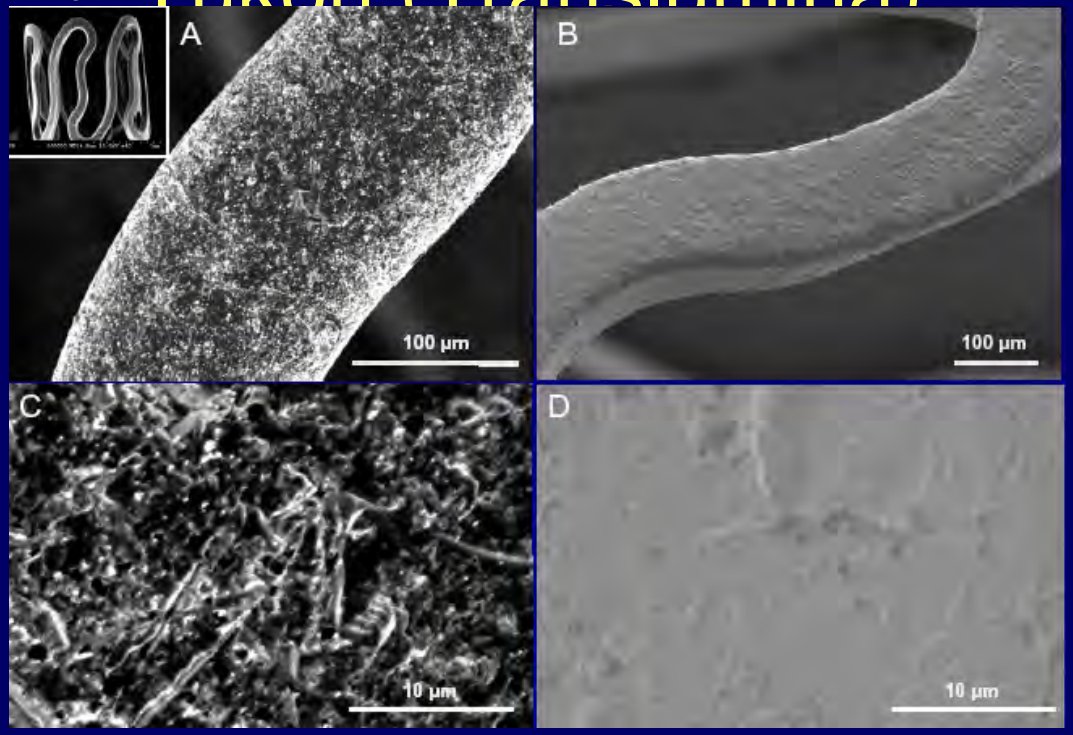
ML VISION®
Stent Delivery
System

SPIRIT
Clinical Trials

Coating Thickness (OD)		
CYPHER®	TAXUS®	XIENCE™ V
7.2 µm	15.6 µm	5.3 µm

New Stents: Microporous

- Yukon (Translumina)



Before

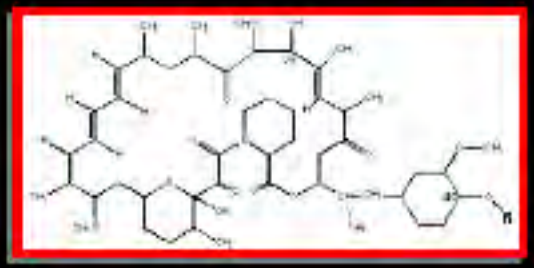
After

BioMatrix™ Stent Components
(Biosensors International Group)

S-Stent™ (stainless steel)
- Quadrature-link design; increased flexibility
- Excellent scaffolding
- Reduced turbulence and wall injury

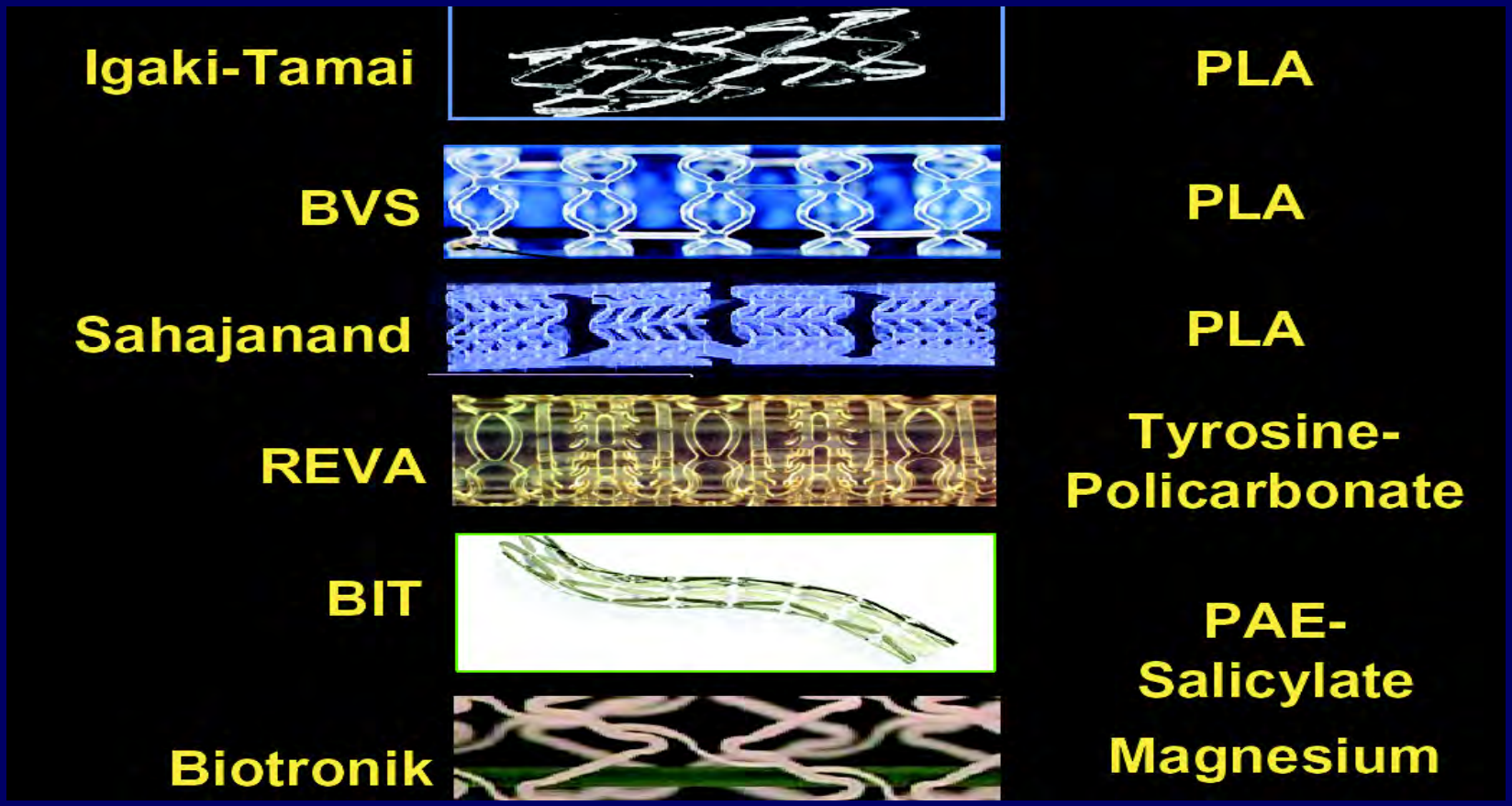
BioFlex I
Biosensors

PLA Polymer
- Uniform thickness; bioresorbable
- Simultaneously releases drug and polymer
- Controlled biodegradability
- High drug-carrying capacity
- Minimizes polymer weight to minimize inflammation; polymer absorbed into tissue

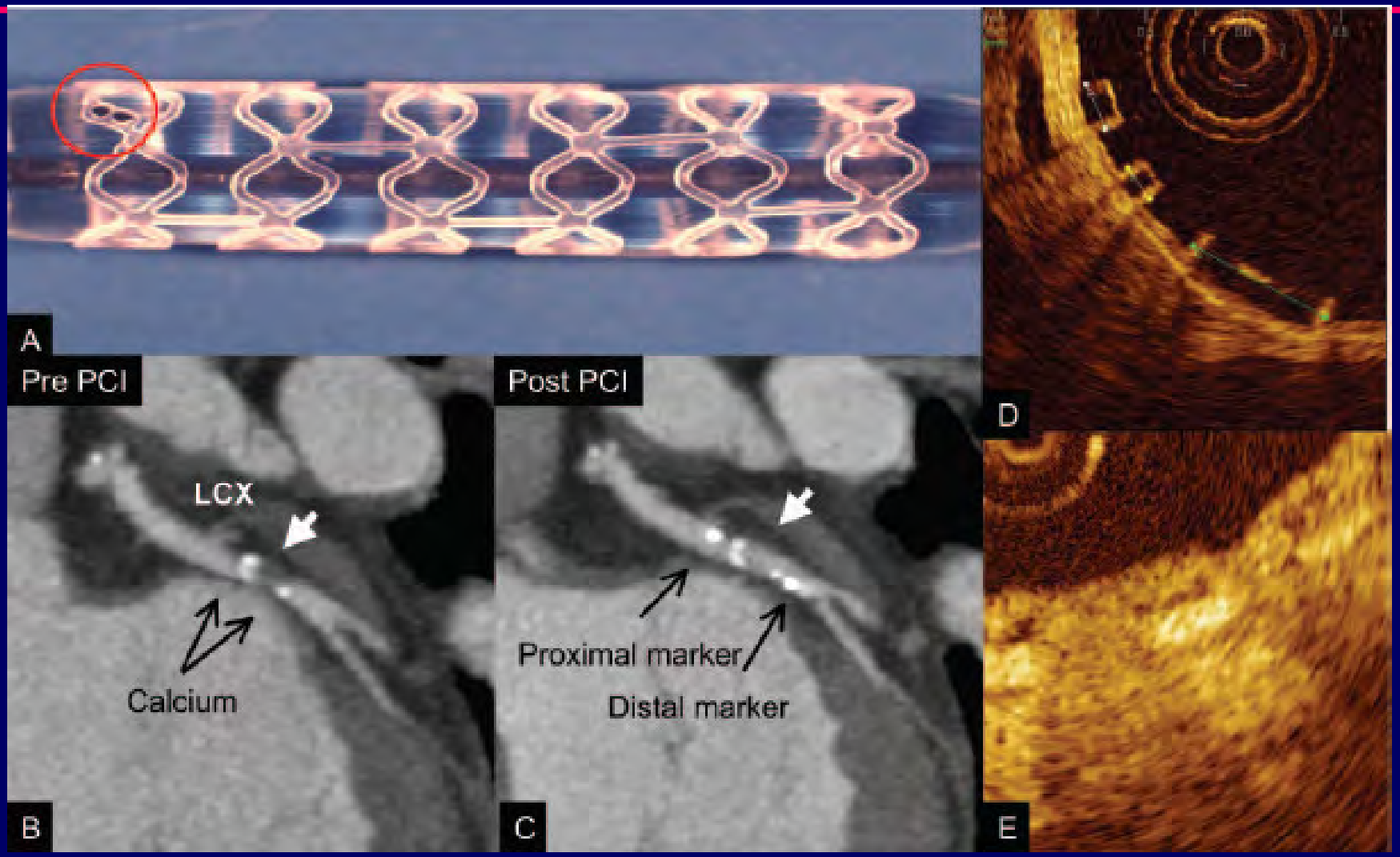


Biolimus A9™ (rapamycin derivative)
- Powerful immunosuppressant, anti-inflammatory
- Prevents smooth muscle cell proliferation
- More lipophilic; elutes faster than rapamycin

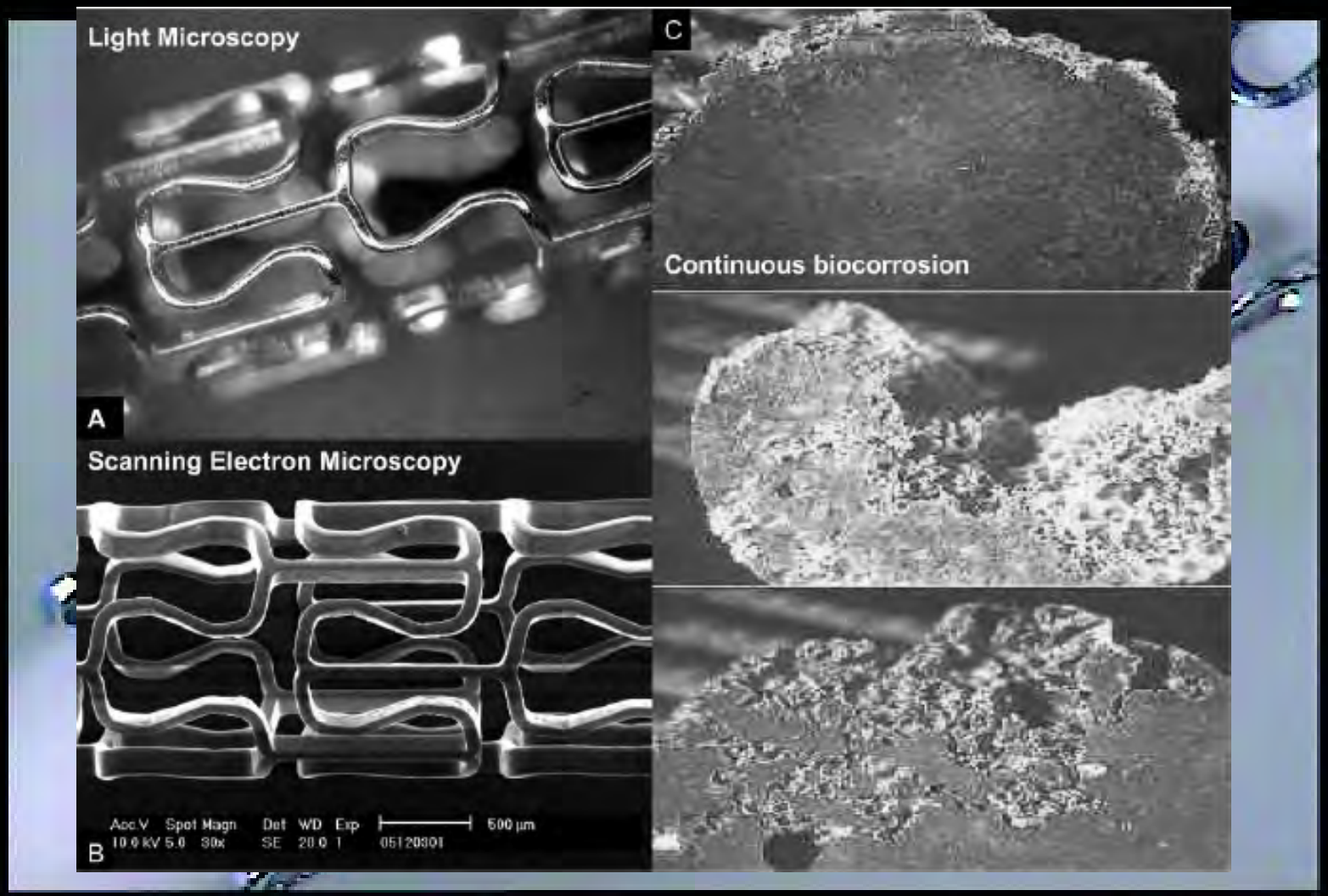
New stents: Bioabsorbable



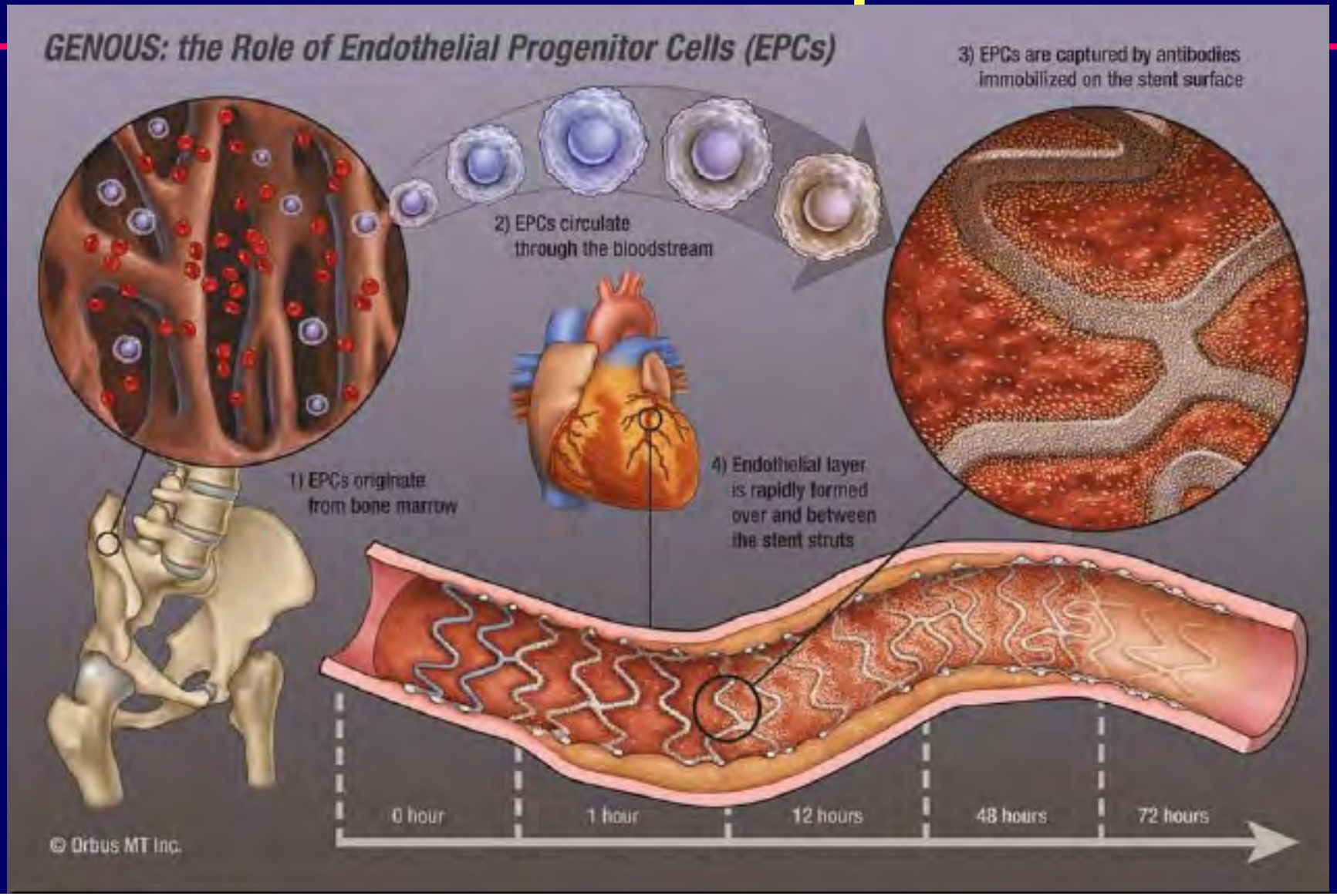
BVS bioabsorbable stent



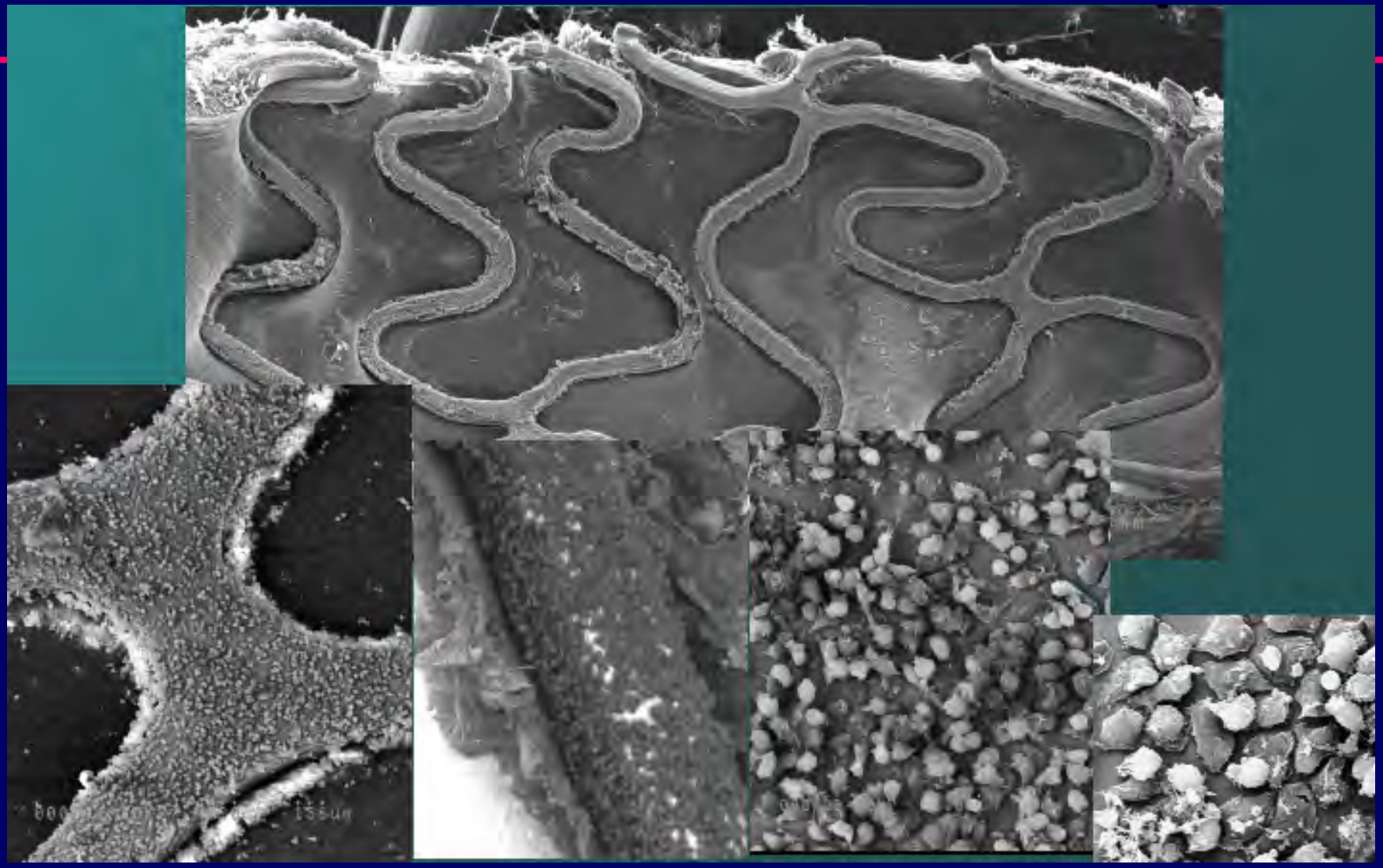
An absorbable metallic magnesium alloy stent



New Stents:
EPC surface capture



EPC capture: 1h.

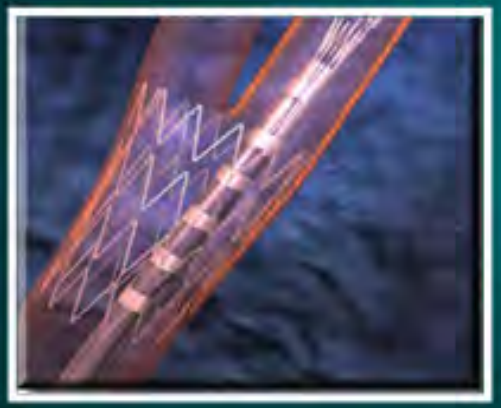


Dedicated Bifurcation Stents

AST petal

Guidant frontier

YMed sidekick



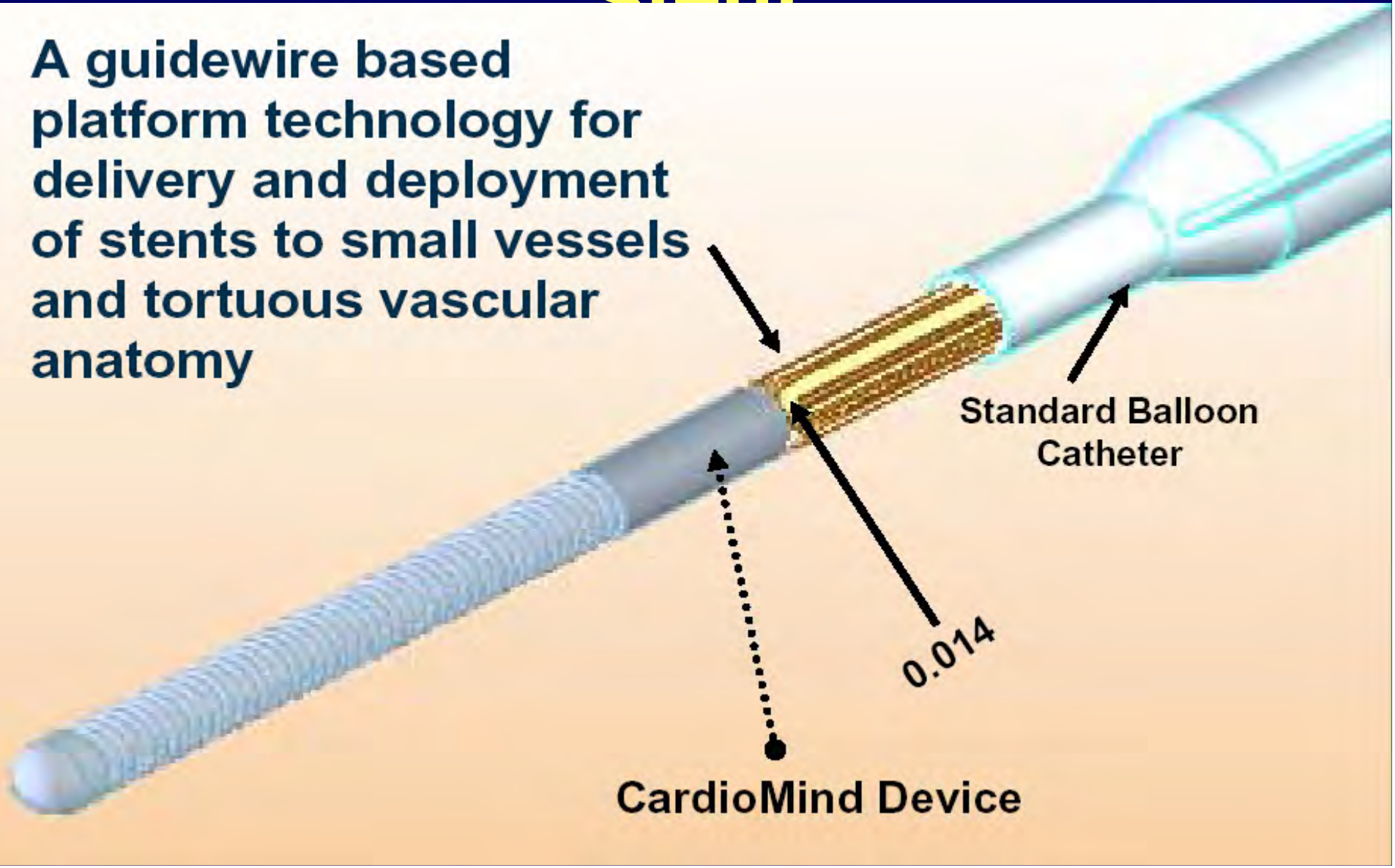
Devax (+ BA9)

"true" bifurcation designs

sidebranch designs

Dedicated small vessel stent

A guidewire based platform technology for delivery and deployment of stents to small vessels and tortuous vascular anatomy



“..There are costs and risks to a program of action but they are far less than the long-range costs and risks of comfortable inaction..”

J.F.K